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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte BORIS KANTOR

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Appeal 2020-002013
Application 15/347,996
Technology Center 1600

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Before DONALD E. ADAMS, JEFFREY N. FREDMAN, and JOHN G. NEW, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134 involving claims to a viral vector. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as the University of South Carolina (*see* Appeal Br. 3).

[2] We have considered the Specification of Nov. 10, 2016 ("Spec."); Final Office Action of Dec. 4, 2018 ("Final Action"); Appeal Brief of July 1, 2019 ("Appeal Br."); and Examiner's Answer of Oct. 21, 2019 ("Ans.").

Statement of the Case

Background

"The ability to alter the function of a targeted gene through genome editing is desirable for both research and therapeutic perspectives" (Spec. ¶ 3). However, "significantly reduced levels of transgene expression in non-integrating systems as compared to integrating systems remains a key issue in developing clinically effective non-integrating gene editing vectors" (*id.* ¶ 7). The Specification teaches "a delivery platform for use in gene editing" that may "include a relatively short, highly efficient promoter that drives transcription of a nucleic acid sequence that encodes a gene-editing molecule, e.g., either a gRNA or a nuclease" (*id.* ¶ 27).

The Claims

Claims 1–7, 9, 10, 12, 15–18, and 20–25 are on appeal. Claim 1 is the sole independent claim, is representative and reads as follows:

> 1. A viral vector comprising:
>
> a region defined between a 5' LTR and either a 3' LTR or a post-transcriptional regulatory element, the region containing no additional LTRs;
>
> a first transcription factor binding element within the region, wherein the first transcription factor binding element is an Sp1 transcription factor binding element or an NF-κB transcription factor binding element;
>
> a promoter within the region, wherein the promoter is an RNA polymerase Ill promoter or an RNA polymerase II promoter; and
>
> a nucleic acid sequence encoding a gene editing molecule within the region and operably linked to the promoter such that the promoter is configured to initiate transcription of the nucleic acid sequence encoding the gene editing molecule.

The Rejections

A. The Examiner rejected claims 1–7, 9, 10, 12, 17, 18, 20, and 22–24 under U.S.C. § 103(a) as obvious over Sanjana,[3] Hioki,[4] Isomura,[5] and LentiCRISPR[6] (Final Act. 3–6).

B. The Examiner rejected claims 15 and 16 under U.S.C. § 103(a) as obvious over Sanjana, Hioki, Isomura, and Wanisch[7] (Final Act. 6–7).

C. The Examiner rejected claims 21 and 25 under U.S.C. § 103(a) as obvious over Sanjana, Hioki, Isomura, and Miyoshi[8] (Final Act. 7–8).

A. 35 U.S.C. § 103(a) over Sanjana, Hioki, Isomura, and LentiCRISPR

The Examiner finds Sanjana teaches a "viral vector system comprising a viral vector comprising a region defined between a 5′ LTR and a 3′ LTR, the region containing no additional LTRs" and that "comprises a U6 promoter (i.e. an RNA polymerase III promoter) . . . operably linked to a nucleic acid sequence encoding a guide RNA (i.e. a gene editing molecule)" (Final Act. 3). The Examiner finds the "promoter is configured to initiate transcription of the nucleic acid sequence encoding the gene editing

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[3] Sanjana et al., *Improved vectors and genome-wide libraries for CRISPR Screening*, 11 Nat. Methods, 783–4 (2014).
[4] Hioki et al., *Efficient gene transduction of neurons by lentivirus with enhanced neuron-specific promoters*, 14 Gene Therapy, 872–82 (2007).
[5] Isomura et al., *Two Sp1/Sp3 Binding Sites in the Major Immediate-Early Proximal Enhancer of Human Cytomegalovirus Have a Significant Role in Viral Replication*, 79 J. Virology 9597–607 (2005).
[6] LentiCRISPR, https://www.addgene.org/52961/, accessed July 7, 2017.
[7] Wanisch et al., *Integration-deficient Lentiviral Vectors: A Slow Coming of Age*, 17 Molecular Therapy 1316–32 (2009).
[8] Miyoshi et al., *Development of a Self-Inactivating Lentivirus Vector*, 72 J. Virology 8150–7 (1998).

molecule" (*id.*). The Examiner acknowledges that "Sanjana does not explicitly teach whether there is a Sp1 transcription factor binding element or a NF-κB transcription factor binding element within the region" (Final Act. 3).

The Examiner finds Hioki teaches lentiviral vectors and that "the addition of human CMV enhancer immediately upstream of the neuron - specific promoter resulted in increased expression levels in all hybrid promoters tested" (Final Act. 3). The Examiner finds "Isomura describes that the proximal enhancer of HMCV contains two Sp1 binding sites as well as a NF-κB binding site" (*id.* at 4).

The Examiner finds it obvious to place "the human CMV enhancer of Isomura immediately upstream of the EFS promoter [of Sanjana] . . . for the advantage of increasing the gene expression of Cas9 as discussed by Hioki who provides clear instructions to use the CMV enhancer to improve the transcriptional activities of cellular promoters" (Final Act. 4).

The issue with respect to this rejection is: Does a preponderance of the evidence of record support the Examiner's conclusion that Sanjana, Hioki, Isomura, and LentiCRISPR render the claims obvious?

Findings of Fact

1. Sanjana teaches "[t]o create a new vector capable of producing higher-titer virus (lentiCRISPRv2), we made several modifications, including removal of one of the nuclear localization signals, human-codon optimization of the remaining nuclear localization signal and P2A bicistronic linker sequences, and repositioning of the U6-driven sgRNA cassette" (Sanjana 783, col. 1–2).

2. Sanjana teaches the viral vector "changes resulted in an approximately tenfold increase in functional viral titer over that of lentiCRISPRv1" (Sanjana 783, col. 2).

3. Sanjana teaches that gene editing molecules "Cas9 (lentiCas9-Blast) and sgRNA (lentiGuide-Puro) are delivered" in the viral vector and that "the single-vector lenti-CRISPRv2 may be better suited for in *vivo* or primary-cell screening applications" (Sanjana 784, col. 1).

4. LentiCRISPR evidences that Sanjana's viral vector includes a CMV early promoter, the human U6 promoter (a RNA polymerase III promoter), guide RNA scaffold for CRISPR/Cas 9 system, and a CMV immediate early enhancer (LentiCRISPR 1, 5).

5. Hioki teaches "[m]any gene delivery vectors have used viral promoters, particularly cytomegalovirus (CMV) or rous sarcoma virus promoter, because they have high transcription activities in all the infected cells" (Hioki 872, col. 1–2). Hioki teaches "it is indispensable to utilize neuron-specific promoters for stable neuron-specific expression" (Hioki 872, col. 2).

6. Hioki "developed novel hybrid promoters by fusing CMV enhancer to neuron-specific promoters, and quantitatively examined their characteristics *in vivo* with VSV-G-pseudotyped lentiviral vectors" (Hioki 876, col. 2).

7. Hioki teaches "[a]fter addition of CMV enhancer to neuron-specific promoters . . . the expression levels were increased by about two- to four-fold in all the hybrid promoters" (Hioki 876, col. 2).

8. Isomura teaches that "[i]n the proximal enhancer of HCMV, there are two Sp1/Sp3 binding sites (GC boxes)" and that the enhancer also

contains NF-κB transcription binding sites (*see* Isomura 9598, col. 1).

9. Isomura teaches the "two Sp1 and Sp3 binding sites located in the MIE proximal enhancer of the HCMV enhanced transcription in transient transfection assay" (Isomura 9601, col. 2)

Principles of Law

The Examiner has the initial burden of establishing a prima facie case obviousness under 35 U.S.C. § 103. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 416 (2007).

Analysis

We adopt the Examiner's findings of fact and conclusion of law (*see* Final Act. 3–6, FF 1–8) and agree that Sanjana, Hioki, Isomura, and LentiCRISPR render claim 1 obvious. We address Appellant's arguments below.

Appellant contends "the vectors described by Sanjana have been designed with multiple modifications as compared to their first-generation vectors, and these modifications have vastly improved the functional viral titer over the first-generation vectors. Therefore, the problem proffered by the Examiner has already been solved by Sanjana" (Appeal Br. 12).

We find this argument unpersuasive because in an obviousness analysis, "[w]e start from the self-evident proposition that mankind, in particular, inventors, strive to improve that which already exists." *Pro–Mold & Tool Co., Inc. v. Great Lakes Plastics, Inc*., 75 F.3d 1568, 1573 (Fed. Cir. 1996). Here, the ordinary artisan would have had reason to further increase

expression levels in the LentiCRISPR vector in order to increase transcription and translation levels, as Hioki explains "[m]any gene delivery vectors have used viral promoters, particularly cytomegalovirus (CMV) or rous sarcoma virus promoter, because they have high transcription activities" (FF 5). Thus, the ordinary artisan, interested in improving expression, would have reasonably considered the superior CMV enhancer (FF 4, 7, 9).[9]

Appellant contends:

> the promoters of Sanjana are simply not equivalent to the promoters of Hioki. The promoters of Sanjana are not neuron-specific promoters (or the more generic type of tissue-specific promoters), and they are not weak in transcription activity. Rather, they are well known in the art of gene editing, and known to function efficiently and precisely in a wide variety of mammalian systems and host cell types by providing a well-defined transcription initiation site for a gene-editing component of a vector.

(Appeal Br. 15).

We find this argument unpersuasive because promoters are a necessary component for gene transcription, and promoter selection is based on a variety of parameters including the cell type (*see, e.g.*, FF 5). As the Examiner finds in the Final Action, Hioki "provides clear instructions to use the CMV enhancer to improve the transcriptional activities of cellular promoters" (Final Act. 4; FF 9). Thus, an artisan interested in using a promoter that functions in a wide variety of cells would select the CMV promoter (FF 5) and would have had reason to further employ CMV

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[9] We also agree with the Examiner's point that improvement to viral titers in Sanjana is not the same as improvements to gene transcription as discussed by Hioki (*see* Ans. 10; *cf.* FF2 and FF 5).

enhancer components that were known to improve transcription of the desired RNA (FF 7, 9).

Appellant contends the "Office has articulated no finding to support a contention that all promoters are considered to be equivalent to one another in the art" (Appeal Br. 15).

We find this argument unpersuasive because the Examiner does not rely on promoter equivalence but rather on the reasoning that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416 (*see* Final Act. 4). Rather, the Examiner finds that the CMV promoter and enhancer are superior choices for improved expression (FF 5, 7, 9).

Appellant asserts:

> the expected results of adding the CMV enhancer element to the highly functioning vector of Sanjana would have been unknown. The vectors of Sanjana have already been modified so as to be highly functioning, and there is simply no support for the suggestion that adding the CMV enhancer to the vectors of Sanjana, which have high functioning promoters, would have the same effect as adding the CMV enhancer to the vectors of Hioki that include tissue-specific and transcriptionally weak promoters.

(Appeal Br. 17).

We find this argument unpersuasive because Hioki teaches the CMV promoter has "high transcription activities in all the infected cells" (FF 5) and both Hioki and Isomura teach that the use of the CMV enhancer results in increased transcription (FF 7, 9). Therefore, both Hioki and Isomura support a general expectation of success in improving transcription using the CMV promoter and enhancer. "Obviousness does not require absolute

predictability of success . . . *all that is required is a reasonable expectation of success*." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009). Appellant provides no evidence, as opposed to argument, that there would not have been a reasonable expectation of success here using well known promoters and enhancers.

Appellant asserts the use of the CMV enhancer "would also be unpredictable as it could lead to the reintroduction of undesirable features in the Sanjana context, such as epigenetic silencing as is known to occur with CMV promoters as discussed in the captioned application" (Appeal Br. 19).

We find this argument unpersuasive for several reasons. First, Appellant does not identify any specific part of the Specification that teaches the use of the CMV enhancer would result in epigenetic silencing. The only apparent disclosure regarding silencing in the Specification occurs in paragraph 7, in the context of negative elements, not shown to be present in the CMV enhancer. Second, this entire argument regarding unpredictability is simply attorney argument without evidence regarding the rejection as presented by the Examiner. *See In re De Blau*we, 736 F.2d 699, 705 (Fed. Cir. 1984)

Conclusion of Law

A preponderance of the evidence of record support the Examiner's conclusion that Sanjana, Hioki, Isomura, and LentiCRISPR render the claims obvious.

B. U.S.C. § 103(a) further including Wanisch or Miyoshi

Appellant does not separately argue these obviousness rejections, instead relying upon their arguments to overcome the combination of

Sanjana, Hioki, Isomura, and LentiCRISPR. We do not find these arguments persuasive for the reasons given above. The Examiner provides sound fact-based reasoning for combining Wanisch and Miyoshi (*see* Final Act. 6–8). Having affirmed the obviousness rejection of claim 1 over Sanjana, Hioki, Isomura, and LentiCRISPR, we also find that the further combinations with Wanisch and Miyoshi renders the rejected claims obvious for the reasons given by the Examiner.

CONCLUSION

In summary:

Claims Rejected	**35 U.S.C. §**	**Reference(s)/Basis**	**Affirmed**	**Reversed**
1–7, 9, 10, 12, 17, 18, 20, 22–24	103	Sanjana, Hioki, Isomura, LentiCRISPR	1–7, 9, 10, 12, 17, 18, 20, 22–24	
15, 16	103	Sanjana, Hioki, Isomura, Wanisch	15, 16	
21, 25	103	Sanjana, Hioki, Isomura, Miyoshi	21, 25	
Overall Outcome			1–7, 9, 10, 12, 15–18, 20–25	

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