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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DOUGLAS J. JOLLY and CARLOS IBANEZ

Appeal 2017–007211
Application 13/376,827
Technology Center 1600

Before TAWEN CHANG, JOHN E. SCHNEIDER, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellants[1] submit this appeal under 35 U.S.C. § 134(a) involving claims to retrovirus producing cell line. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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[1] Appellants identify the Real Party in Interest as Tocagen Inc. App. Br. 2.

STATEMENT OF THE CASE

Appellants' "disclosure relates to methods for producing recombinant replication competent retroviral vectors" and "cell lines useful for producing such vectors." *Id.* ¶ 2. As background, the Specification explains:

> A retroviral RNA genome usually comprises 6 typical regions leading to the expression of multiple proteins. These region[s] include the *gag*, *pol* and *env* gene sequences associated with a packaging signal, a psi (ψ) signal flanked by 5' and/or 3' long terminal repeats (LTR) regions. . . .
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> ***
>
> Because of their ability to form proviruses, retroviruses are useful to modify the genome of a target or host cell and various modifications have been made to retroviruses for use in gene therapy. Gene therapy using retroviral vectors is generally performed by adding a heterologous polynucleotide to the viral genome which encodes or produces a polypeptide or transcript of interest, packaging the recombinant genome into a viral particle and infecting a target host cell. The target cell will then incorporate the exogenous gene as being a part of a provirus.

Id. ¶¶ 5–6.

The Specification explains that "[m]ost retroviral vectors have been rendered 'defective' to avoid uncontrolled spread and production of virions." *Id.* ¶ 7. The invention, on the other hand, relates to "cell lines and viral particle producing cells useful for producing recombinant *replication competent* retroviral vectors for gene therapy." *Id.* ¶ 8 (emphasis added). A replication-competent retrovirus (or "RCR") "is a viral particle that has the capacity to replicate by itself in a host cell." *Id.* ¶ 39.

Claims 1, 4–8, 10, 14, 16–36, 39, 40, 45–47, 49–55, 57, and 58 are on appeal. Claim 1 is illustrative and are reproduced below:

> 1. A retrovirus producing cell line for the production of a replication competent retrovirus particle, the cell line comprising a fibrosarcoma cell line said cell line stably expressing a recombinant retroviral genome comprising Long-Terminal Repeat (LTR) sequences at the 3' end of the retroviral polynucleotide sequence, a promoter sequence at the 5' end of the retroviral polynucleotide, a *gag* nucleic acid domain, a *pol* nucleic acid domain and an *env* nucleic acid domain, a cassette comprising an internal ribosome entry site (IRES) or regulatory nucleic acid domain operably linked to a heterologous polynucleotide, wherein the cassette is positioned 5' to the 3' LTR and 3' to the *env* nucleic acid domain, and cis-acting sequences necessary for reverse transcription, packaging and integration, wherein the cell line has been conditioned to be grown and continually passaged in serum free media and in non-adherent suspension, and wherein viral particle produced from the cell line are stable and without a significant decrease in titer or infectivity when stored for 12 months at ≤-65°C as measured by qPCR.

App. Br. 18 (Claims App.).

The claims stand rejected as follows:

I. Claims 1, 4–8, 14, 16–19, 24, 49, and 51–57 under 35 U.S.C. § 103(a) as obvious over Hiraoka,[2] Hartl,[3] and Birch.[4]

II. Claims 10, 20–23, 25, 30–32, 34–36, 39, 40, 45, and 46 under 35 U.S.C. § 103(a) as obvious over Hiraoka, Hartl, Birch, and Kasahara.[5]

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[2] Kei Hiraoka et al., *Tumor-Selective Gene Expression in a Hepatic Metastasis Model after Locoregional Delivery of a Replication-Competent Retrovirus Vector*, 12 CLIN CANCER RES 7108–7116 (2006).
[3] I. Hartl et al., *Library-based selection of retroviruses selectively spreading through matrix metalloprotease-positive cells*, 12 GENE THERAPY 918–926 (2005).
[4] Birch et al., US 2005/0084928 A1, published Apr. 21, 2005.
[5] Kasahara, US 2008/0008685 A1, published Jan. 10, 2008.

III. Claim 26 under 35 U.S.C. § 103(a) as obvious over Hiraoka, Hartl, Birch, GenBank,[6] and Miyagi.[7]

IV. Claim 50 under 35 U.S.C. § 103(a) as obvious over Hiraoka, Hartl, Birch, and Jin.[8]

V. Claim 58 under 35 U.S.C. § 103(a) as obvious over Hiraoka, Hartl, Birch, and Benedict.[9]

An oral hearing before the Board related to this appeal took place on November 1, 2018.

REJECTIONS I–V (OBVIOUSNESS)

Issue

Each of Rejections I–V, and Appellants' arguments about the same, hinge on whether the combination of Hiraoka, Hartl, and Birch makes obvious the retrovirus producing cell line as recited in claim 1. Ans. 3–8; App. Br., *passim*. Rejections II–V rely on the same Hiraoka, Hartl, and Birch combination and then rely on further art solely as teaching certain limitations of the dependent claims. Ans. 8–12. Rejection II, for example, further relies on Kasahara's disclosure of a tissue-specific promoter as

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[6] GenBank: AAG33626.1 (Nov. 21, 2000).
[7] Tohru Miyagi et al., *Gene therapy for prostate cancer using the cytosine deaminase/uracil phosphoribosyltransferase suicide system*, 5 J GENE MED 30–37 (2003).
[8] Yan Jin and J. A. Cowan, *Targeted Cleavage of HIV Rev Response Element RNA by Metallopeptide Complexes*, 128 J. AM. CHEM. SOC. 410–411 (2006).
[9] William F. Benedict et al., *Tumorigenicity of Human HT1080 Fibrosarcoma x Normal Fibroblast Hybrids: Chromosome Dosage Dependency*, 44 CANCER RESEARCH 3471–3479 (1984).

addressing limitations in dependent claim 10 that the Examiner finds are not taught by the Hiraoka, Hartl, and Birch combination. *Id.* at 9.

The dispositive issue here is whether the Examiner established by a preponderance of the evidence that the claimed retrovirus producing cell line would have been obvious over Hiraoka, Hartl, and Birch.

Analysis

The Examiner concludes that claim 1 would have been obvious over Hiraoka, Hartl, and Birch. Ans. 3–7. The Examiner finds that Hiraoka teaches an adenocarcinoma cell line (WiDr) that produces a replication competent murine leukemia virus (MLV), having a recombinant retroviral genome encompassed by the retroviral genome recited in claim 1. *Id.* at 4 (citing Hiraoka, Fig. 1 (depicting a genome with the particular sequences, domains, cassette, and positional arrangement of the same as claimed)). The Examiner finds, however, that "Hiraoka does not teach that a replication competent retrovirus can be stably produced fibrosarcoma cell line that has been conditioned to be grown in serum free medium and in suspension." *Id.* at 4. Accordingly, the Examiner turns to Hartl and Birch. *Id.* at 4–5.

The Examiner finds that Hartl teaches a fibrosarcoma cell line (HT1080) that produces a murine leukemia virus construct. *Id.* at 4 (citing Hartl, Figs. 1 and 3). According to the Examiner, "Hartl implies that the retrovirus produced is replication competent by indicating that viruses can be produced . . . and then used in infecting and spreading in HT1080 cells." *Id.*; *see also id.* at 4–5 (citing Figs. 3 and 4 as showing stable production of certain virus particles for up to 20 days).

Because the Examiner finds that "neither Hiraoka nor Hartl teach that the cell line has been conditioned to be grown in serum free medium and in non-adherent suspension," as required in claim 1, the Examiner cites Birch.

Ans. 5. According to the Examiner, Birch "teaches that HT1080 cells could be adapted to growth in non-adherent suspension and serum free medium." *Id.* at 5 (citing Birch ¶ 52).

The Examiner concludes it would have been obvious to substitute the HT1080 cells of Hartl with those of Birch, or otherwise adapt the HT1080 cells so they are conditioned to be grown and continually passaged in serum-free media and in a non-adherent suspension. *Id.* at 5–6. The Examiner reasons that the ordinarily skilled person would have been motivated to make this change "to cut the cost of serum purchasing and to establish a large volume continuous growth condition in suspension." *Id.* The Examiner asserts that, because Hartl's and Hiraoka's retroviruses are "highly similar," it would have been obvious to introduce Hiraoka's retrovirus into the substituted or adapted HT1080 cell line. *Id.* at 6. According to the Examiner, "[t]he expectation of successfully establishing a HT1080 cell line stably producing the retrovirus of Hiraoka is high since both HT1080 and WiDr cell lines have been shown to be able to stably produce replication competent retrovirus MLV." *Id.*

As for claim 1's final clause, reciting "wherein viral particle produced from the cell line are stable and without a significant decrease in titer or infectivity when stored for 12 months at ≤-65°C as measured by qPCR," the Examiner finds this is a latent property of the prior art. *Id.* at 7. According to the Examiner, mere recognition of this property by the Appellants does not render nonobvious an obvious invention. *Id.*

It is the Examiner's burden to establish a *prima facie* case of unpatentability, including on the issues of motivation for modifying the prior art and a reasonable expectation of success in making such a modification in order to support the conclusion of obviousness. *In re Oetiker*, 977 F.2d

1443, 1445 (Fed. Cir. 1992). We are unpersuaded that the burden has been met. On the present record, the Examiner did not provide sufficient evidence or persuasive technical reasoning to demonstrate why the skilled person would have predictably used the retrovirus of Hiraoka in HT1080 cells (of Hartl or Birch) with a reasonable expectation of successfully yielding a cell line that produces stable, infective, and replication competent retrovirus particles as claimed.

As Appellants point out, Hartl relates to a method of library-based selection of retroviruses and teaches that viral uptake and spreading capacity are *highly cell-type specific*. App. Br. 8; Reply Br. 5 ("Hartl *et al.* further teach that these selected viral clones can have vastly different efficiencies based on which cell type is used."). As Hartl observed, "[o]ne of the most interesting outcomes of this study was the observation how strongly the selection is influenced by the cell type applied in the selection procedure." Hartl, 923; App. Br. 8.

Hartl determined that certain MLV viral clones encoding certain linker peptides provided efficient viral spreading in HT1080 cells (a fibrosarcoma cell line) and U87-MG cells (a glioma cell line). Hartl, 923 ("[T]he U87-MG-selected C-HV-A virus reached almost WT [wild type] virus efficiency in spreading through U87-MG cells and thus was much more effective than the C-AK-A virus selected on HT1080 cells."); App. Br. 8; Reply Br. 5–8. As Appellants note, Hartl discloses that some specifically engineered retroviruses (e.g., C-AK-A) are capable of infecting and spreading in HT1080 cells. Reply Br. 7–8; *see also* Hartl, 919 (Fig. 1), 921 (Fig. 3). Other MLV-based retroviruses, however, provided little or no virus spreading in HT1080 cells. Hartl, 920 ("Infection with the C-A virus did not result in RT activity above background level.").

Based on the evidence and reasoning of record, the Examiner has not made a sufficient showing that a skilled person at the time of the invention would have reasonably expected that Hiraoka's retrovirus would spread effectively in the HT1080 cells of either Hartl or Birch. Hartl, in fact, demonstrates that genetically similar retrovirus clones derived from MLV behave quite differently in different cell types — some infected and spread in HT1080 cells, and others did not. Hartl, 919 (Fig. 1), 921 (Figs. 3–4, Table 2). Accordingly, the Examiner's conclusory assertion that the retrovirus of Hiraoka is "highly similar" to those in Hartl as justifying the reasonable expectation of success does not, without more, hold up here. Appellants contend that, based on Hartl, a process of re-selecting Hiraoka's retroviruses in HT1080 cells, and generating retroviral clones potentially optimized for production in HT1080 cells, would present a large and unpredictable experimental hurdle. Reply Br. 8.[10] And, on the present record, we agree.

Conclusion of Law

For the reasons above, we conclude that the preponderance of the evidence on this record does not support the Examiner's rejection of claim 1 as obvious over Hiraoka, Hartl, and Birch. The rejection is, thus, reversed. For substantially the same reasons, we also reverse the remainder of

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[10] The present rejection does not propose specific changes to, or engineering of, Hiraoka's retrovirus to render it suitable for use in HT1080 cells. Rather, the Examiner appears to be of the view that because that virus worked as an RCR in WiDr cells, it would be expected to provide that function in HT1080 cells. *See* Ans. 6. As we explained, however, Hartl evidences that MLV-based retroviruses and cell types are not functional equivalents or so simply interchangeable as the Examiner's reasoning would suggest.

Rejection I (for claims 4–8, 14, 16–19, 24, 49, and 51–57) and Rejections II–V. The Examiner has not shown that the other cited art makes up for the deficiencies of the Hiraoka, Hartl, and Birch combination, on which the other rejections rely.

SUMMARY

We reverse the rejections for obviousness on appeal.

REVERSED