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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/221,265	07/27/2016	Seppo YLA-HERTTUALA	Trizell - GB07/02695.8	5263

22925 7590 01/31/2020

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
01/31/2020	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SEPPO YLA-HERTTUALA, KARI J. AIRENNE, and HANNA P. LESCH[1]

Appeal 2019-001329
Application 15/221,265
Technology Center 1600

Before ERIC B. GRIMES, JEFFREY N. FREDMAN, and JOHN E. SCHNEIDER, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims related to lentiviral vectors, which have been rejected on several grounds. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

STATEMENT OF THE CASE

"According to the present invention, a method of generating a lentivirus vector[] comprises cloning each of a lentivirus transfer construct, *gag*, *pol*, an envelope protein and *rev* respectively into the same or different

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[1] Appellant identifies the real party in interest as Trizell Limited. Appeal Br. 1. We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a).

baculoviruses, and transducing a producer cell with the or each baculovirus." Spec. 2:18–21.

Claims 1–17 are on appeal. Claims 1, 8, and 12, reproduced below, are the independent claims:

1. A method comprising:

a. Transducing a mammalian cell *in vitro* with a recombinant baculovirus comprising a transfer construct comprising a packaging genome of a second virus along with a therapeutic transgene to make a transduced mammalian producer cell comprising a transfer construct containing the packaging genome of the second virus along with the therapeutic transgene; and then

b. Culturing said transduced mammalian producer cell in culture media, and harvesting from said transduced mammalian producer cell and/or culture media the second virus having the therapeutic transgene.

8. A mammalian cell transduced by a recombinant baculovirus having at least one nucleic acid sequence coding for a second virus obtained from a virus which in its wild state has a single stranded genome, said second virus being replication-deficient and having a therapeutic transgene.

12. A mammalian producer cell transduced with a recombinant baculovirus, said mammalian producer cell producing viral vector able to transfect a human cell which is not actively dividing, said viral vector produced by a said mammalian producer cell being substantially free of insect cell membrane.

The claims stand rejected as follows:

Claims 1–7 and 11–17 under 35 U.S.C. § 112, second paragraph, as indefinite (Final Action[2] 6–7);

Claims 1–8 and 12–17 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description (Final Action 3);

Claims 9 and 10 under 35 U.S.C. § 112, fourth paragraph, as being in improper dependent form (Final Action 10);

Claims 1–17 under 35 U.S.C. § 102(b) as anticipated by Leblois-Prehaud[3] (Final Action 11);

Claims 15–17 under 35 U.S.C. § 102(b) as anticipated by Schauber[4] (Final Action 18);

Claims 1–17 under 35 U.S.C. § 103(a) as obvious based on Schauber, Leblois-Prehaud, and Kingsman[5] (Final Action 20); and

Claims 1–14, provisionally, for obviousness-type double patenting based on claims 1–7 and 10 of application 12/522,646 (Final Action 35–36).

OPINION

Definiteness

"Packaging genome"

The Examiner concludes that the metes and bounds of claim 1 are unclear because the claim recites "a packaging genome of a second virus." Final Action 7. The Examiner speculates that this limitation could refer to "a

[2] Office Action mailed March 14, 2018.
[3] US 6,387,670 B1; issued May 14, 2002.
[4] US 6,863,884 B2; issued Mar. 8, 2005.
[5] WO 98/55640; published Dec. 10, 1998.

genome of a second virus to be packaged or an already packaged genome of a second virus." *Id.* The Examiner states that the limitation was interpreted, for purposes of examination, "to refer to a genome of a second virus to be packaged in the mammalian producer [cell]." *Id.*

Appellant argues that "[a] packaging genome is what the name suggests - a *genome* (set of genes) coding for the various polypeptides required to *package* the virus. The instant application describes one at *e.g.*, 2:19–20, in teaching *gag-pol*. . . . *gag-pol* is a packaging genome. The artisan understands this." Appeal Br. 4.

We agree with the Examiner that claim 1 is indefinite. The Specification does not include the term "packaging genome." The sentence including the passage pointed to by Appellant as a description of a packaging genome reads as follows: "According to the present invention, a method of generating a lentivirus vector, comprises cloning each of a lentivirus transfer construct, *gag*, *pol*, an envelope protein and *rev* respectively into the same or different baculoviruses, and transducing a producer cell with the or each baculovirus." Spec. 2:18–21.

This passage describes a lentivirus transfer construct, *gag*, and *pol* as three different components that can be cloned either into the same baculovirus or into different baculoviruses, which can be transduced into a producer cell in order to generate a lentivirus vector. Claim 1, however, recites a "baculovirus comprising a transfer construct," where the "transfer construct compris[es] a packaging genome of a second virus." The cited passage does not describe a transfer construct as comprising any of the other recited genes, nor does it describe *gag* and *pol* as a packaging genome.

Claim 1 does not state that the recited packaging genome includes or requires *gag* and *pol*, nor does the Specification support that interpretation, since the passage that Appellant points to states that *gag* and *pol* can be cloned into different baculoviral vectors, and suggests that each of (a) a lentivirus transfer construct, (b) *gag*, (c) *pol*, (d) an envelope protein, and (e) *rev*, are transduced into a producer cell in the disclosed method. *See also* Spec. 2:29–30 ("To perform the method of the invention, the baculovirus(es) must comprise a lentivirus transfer construct, *gag*, *pol*, a suitable envelope protein and *rev*."). The cited description therefore does not support Appellant's position that a skilled artisan would recognize that *gag* and *pol* are a "packaging genome" because they encode the polypeptides required to package a virus.

In addition, claim 1 is not limited to a method in which the "second virus" is a lentivirus, while the passage in the Specification that Appellant points to specifically describes a "method of generating a *lentivirus* vector." Spec. 2:18–19 (emphasis added). Thus, even if the evidence supported Appellant's argument that a skilled artisan would recognize *gag-pol* as an example of a packaging genome, the record provides no guidance regarding what a "packaging genome" means in the context of viruses other than lentiviruses.

In summary, Appellant has not pointed to a specific definition of a "packaging genome" in the Specification, nor has Appellant pointed to evidence showing that "packaging genome" has a specific definition that is known and accepted by those skilled in the art. Therefore, the scope of claim 1, even when read in light of the Specification, is unclear. The rejection of

claim 1 under 35 U.S.C. § 112, second paragraph, is affirmed. Claims 2–7 depend from claim 1 and are indefinite for the same reason.

Claim 11

The Examiner states that, "[i]n claim 11, it is unclear what is encompassed by the limitation 'Obtaining the recombinant baculovirus of Claim 8'. It is not[ed] that **claim 8 is now directed to a mammalian cell** transduced by a recombinant baculovirus." Final Action 7.

Appellant "does not here appeal the rejection of claim 11 as unclear." Appeal Br. 5. We therefore affirm the rejection of claim 11 under 35 U.S.C. § 112, second paragraph.

"Substantially free"

The Examiner concludes that claim 12 is indefinite because the term "substantially free" is a relative term that "is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." Final Action 7.

Appellant argues that the "instant inventors teach to express virus in human producer cells. *See Specification* 7:2. The resulting virus is thus enveloped in human cell membrane." Appeal Br. 5. Appellant also points out that "'[s]ubstantially free' . . . reads on no insect membrane at all." *Id.* at 6.

We reverse this basis of the rejection. Terms of degree are not per se indefinite. "Such broadening usages as 'about' must be given reasonable scope. . . . Although it is rarely feasible to attach a precise limit to 'about,'

the usage can usually be understood in light of the technology embodied in the invention." *Modine Manufacturing Co. v. U.S. ITC*, 75 F.3d 1545, 1554 (Fed. Cir. 1996).

Here, the Examiner has not disputed Appellant's position that a viral vector produced by a mammalian cell, as recited in claim 12, would be expected to be enveloped in human cell membrane, and thus would be expected to be entirely free of insect cell membrane. In fact, the Examiner stated that "it is unclear how a produced viral vector in a mammalian cell transduced with a recombinant baculovirus in claim 12 would even contain any minute amount of an insect cell membrane." Final Action 8. This statement confirms that those skilled in the art would have no reason to expect the viral vector produced by the cell of claim 12 to comprise any insect cell membrane.

In short, the disputed limitation merely states that the viral vector produced by the claimed cell is "substantially" free of a contaminant that would not be expected to be present at all, and therefore does not make the scope of the claimed mammalian producer cell unclear to those of ordinary skill in the art.

Claims 12–14

Claims 12–14 stand rejected as indefinite, on the basis that they omit essential elements, specifically "a recombinant baculovirus encoding a genome of a viral vector/virus comprising a transgene along with the necessary components for packaging said viral vector/virus (e.g., gag, pol, rev, env for a lentiviral vector)." Final Action 8.

Appellant argues that, although "[c]laim 12 is broader than the inventors' specific examples," and "many of the specific embodiments in the examples are not mentioned in claim 12," the elements of claim 12 interrelate and therefore the claim is not indefinite. Appeal Br. 7–8.

We reverse this basis of the rejection. Claim 12 recites the structural limitations of (a) a "mammalian producer cell," (b) "transduced with a recombinant baculovirus," and the functional limitations that (c) the cell "produc[es] viral vector able to transfect a human cell which is not actively dividing," and (d) the "viral vector produced by a [sic] said mammalian producer cell [is] substantially free of insect cell membrane."

The Examiner has not explained why a skilled artisan would be unable to determine which mammalian cells are encompassed by the claim language. *See In re Schreiber*, 128 F.3d 1473, 1478 (Fed. Cir. 1997) ("A patent applicant is free to recite features of an apparatus either structurally or functionally. *See In re Swinehart,* . . . 439 F.2d 210, 212 . . . (CCPA 1971) ('[T]here is nothing intrinsically wrong with [defining something by what it does rather than what it is] in drafting patent claims.')." (bracketed material in original)). While the functional limitations of claim 12 might make the claim broader than it would be if it included the limitations suggested by the Examiner, "breadth is not to be equated with indefiniteness." *In re Miller*, 441 F.2d 689, 693 (CCPA 1971).

"Obtaining the viral vector . . ."

Claims 15–17 stand rejected as indefinite, on the basis that it is unclear what is encompassed by "[o]btaining the viral vector" of one of claims 12–14. Final Action 8. The Examiner notes that claims 12–14 are

directed to "**a mammalian producer cell** transduced with a recombinant baculovirus to produce a viral vector able to transfect a human cell which is not actively dividing," and states that it is unclear whether the obtained viral vector is in the form of a mammalian producer cell or is free of the mammalian producer cell. *Id.*

The Examiner states that, for purposes of prosecution, the limitation will be interpreted "to refer to any viral vector that is produced/generated from a mammalian producer cell transduced with a recombinant baculovirus encoding necessary components/elements for said viral vector." *Id.* at 8–9. Appellant agrees that this interpretation of the claim language is correct. Reply Br. 5[6] ("Appellants do not disagree with the Examiner's suggested interpretation.").

In short, the Examiner and Appellant agree that "obtaining the viral vector" of claims 12–14, as recited in claims 15–17 respectively, means obtaining the viral vector that is produced by the mammalian producer cell defined by claims 12–14. We therefore reverse the rejection of claims 15–17 under 35 U.S.C. § 112, second paragraph.

Written Description

"Packaging genome"

Claims 1–7 stand rejected as lacking adequate written description, because the recitation of transducing a mammalian cell with a "recombinant baculovirus comprising a transfer construct comprising a packaging genome of a second virus along with a therapeutic transgene" (claim 1), encompasses

[6] After page 1, the pages of the Reply Brief are unpaginated but we refer to them as if they were consecutively numbered beginning with page 1.

"transducing a mammalian cell *in vitro* with a recombinant baculovirus comprising **a transfer construct comprising a genome of a second virus that is already packaged (packaging genome)** along with a therapeutic transgene to make a transduced mammalian producer cell." Final Action 3–4.

> The Examiner finds that the Specification does not describe
>
> **a transfer construct comprising an already packaged/packaging genome of a second virus**. This is evident by the teachings of the instant specification that disclose that **the mammalian producer cell is also transduced with recombinant baculovirus(es) encoding a suitable envelope protein, gag, pol and rev to generate functional and packaged lentiviruses**.

Id. at 4.

Appellant argues that "none of the claims mention 'already-packaged packaging genome,' much less require one." Appeal Br. 8.

We will affirm this basis of the rejection. It is true that none of the claims on appeal states that a "packaging genome" encompasses a packaged viral genome, or part of one. However, as discussed above, neither the claims nor the Specification make clear what is required or excluded by the term "packaging genome."

In its arguments regarding definiteness, in fact, Appellant seems to suggest that "packaging genome" is broad enough to encompass a packaged viral genome, or at least part of one. *See* Reply Br. 1: "[T]he Examiner argues that the term ["packaging genome"] 'may imply a genome that is packaged.' The Examiner is correct: the term 'packaging genome' encompasses a packaging genome which is in a viral capsid."

Under that apparently agreed-upon interpretation, claim 1 encompasses a method of transducing a mammalian cell with a recombinant baculovirus comprising a transfer construct that itself comprises a packaging genome (of a second virus) *in a viral capsid*.

Regarding this embodiment, Appellant argues that,

> assuming the claims required it, the specification in fact teaches an "already-packaged packaging genome." *gag-pol* is a packaging genome. The specification teaches to put *gag-pol* on a plasmid (pBAC-*gag-pol*) . . . [and] to package that plasmid in a baculovirus. pBAC-*gag-pol* packaged in baculovirus thus becomes an "already-packaged packaging genome."

Appeal Br. 8–9.

This argument is unpersuasive because, as discussed above with respect to claim definiteness, the evidence of record does not support Appellant's position that a skilled artisan would recognize *gag-pol* as a "packaging genome." In addition, and even if *gag-pol* were recognized as one example of a packaging genome, claim 1 requires not simply a baculovirus comprising a packaging genome, but a baculovirus comprising a *transfer construct* that comprises a packaging genome. Even under Appellant's interpretation, therefore, the description that is relied upon does not describe the disputed claim limitation. We therefore affirm the rejection of claim 1, and dependent claims 2–7, under 35 U.S.C. § 112, first paragraph, for lack of adequate written description.

Claim 8

The Examiner reasons that the recitation in claim 8 of "'[**a**] **mammalian cell transduced by a recombinant baculovirus**' . . . encompasses any mammalian cell, including a mammalian cell ***in vitro*** . . .

and ***in vivo*** (e.g., **a mammalian cell in an animal**)," as long as it includes the nucleic acid recited in claim 8. Final Action 4. The Examiner finds that "[t]he as-filed specification at best has a written support for an *in vitro* mammalian cell being transduced with a recombinant baculovirus." *Id.* at 5.

Appellant points to the "Summary of claimed subject matter" section of the Appeal Brief for the argument with respect to this rejection: "Applicant's brief says that mammalian cell is supported in the specification at e.g., 2:6–7, 1:14 and 4:5, and transduction with recombinant baculovirus is supported in the specification at e.g., 3:15–16. *See Appeal Brief* (July 2018) at 2:25–26." Reply Br. 6.

We affirm the rejection. For written description, "an adequate prima facie case must . . . sufficiently explain to the applicant what, in the examiner's view, is missing from the written description. . . . When no such description can be found in the specification, the only thing the PTO can reasonably be expected to do is to point out its nonexistence." *Hyatt v. Dudas*, 492 F.3d 1365, 1370 (Fed. Cir. 2007). Here, the Examiner has pointed out that, while the Specification describes mammalian cells transduced with baculovirus in vitro, a description of such cells in vivo is missing from the Specification. Final Action 4–5.

The burden is then shifted to Appellant "to cite to the examiner where adequate written description could be found, or to make an amendment to address the deficiency." *Hyatt v. Dudas*, 492 F.3d at 1371. Appellant has pointed to the Specification at page 1, line 14; page 2, lines 6–7; page 3, lines 15–16; and page 4, line 5. Reply Br. 6.

We have reviewed the cited passages in the Specification but fail to find any description of a mammalian cell in vivo, transduced with a recombinant baculovirus. Appellant therefore has failed to identify written descriptive support for the limitation the Examiner finds to be missing from the Specification. We affirm the rejection of claim 8 under 35 U.S.C. § 112, first paragraph.

"Substantially free of insect cell membrane"

The Examiner reasons that the recitation in claim 12 of a viral vector "substantially free of insect cell membrane" encompasses

> an embodiment of **a viral vector produced by a mammalian producer cell containing/comprising a minute amount of insect cell membrane (substantially free of insect cell membrane does not mean completely free of insect cell membrane)**. There is **no written support** in the as-filed specification for this embodiment encompassed by the new limitation.

Final Action 5.

Appellant again points to the "Summary of claimed subject matter" section of the Appeal Brief for the argument with respect to this rejection: "Applicant's brief says that viral vector is supported in the specification at e.g., Figure 2, mammalian producer cell is supported in the specification at e.g., 2:6–7, 1:14 and 4:5, and substantially free of insect cell membrane is supported in the specification at e.g., 8:8. *See Appeal Brief* (July 2018) at 3:3–8." Reply Br. 7.

We have reviewed Figure 2 and the cited passages in the Specification but fail to find any description of a viral vector, produced by a mammalian producer cell, comprising any amount of insect cell membrane. Appellant

therefore has failed to identify written descriptive support for the limitation the Examiner finds to be missing from the Specification. We affirm the rejection of claim 12, and dependent claims 13–17, under 35 U.S.C. § 112, first paragraph.

Dependent claim format

Claims 9 and 10 stand rejected as being in improper dependent form, because they are directed to the "recombinant baculovirus of claim 8," while claim 8 is directed to a "mammalian cell transduced by a recombinant baculovirus." Final Action 10. The Examiner thus finds that claims 9 and 10 do not include all of the limitations of claim 8, from which they depend. *Id.*

Appellant agrees that the preambles of claims 9 and 10 have a typographical error. Reply Br. 7. We therefore affirm the rejection of claims 9 and 10 under 35 U.S.C. § 112, fourth paragraph.

Anticipation by Leblois-Prehaud

The Examiner finds that Leblois-Prehaud discloses

> **a method for producing any recombinant virus (e.g., adenovirus, adeno-associated virus and retrovirus) based on the use of one or more baculoviruses for providing the complementary functions** . . . **for the defective recombinant genome in competent host cells such as 293 cells and derivatives thereof, and purifying the recombinant virus in the supernatant of competent host cells**.

Final Action 11–12.

The Examiner finds that Leblois-Prehaud also discloses that "**a recombinant viral genome (e.g., an exemplary defective recombinant adenovirus, including replication defective recombinant minimum adenovirus or adenovirus defective for E1 and E3) can also be**

introduced into competent host cells in the form of another recombinant baculovirus," and that the recombinant viruses produced in its method can include therapeutic transgenes. *Id.* at 12. The Examiner concludes that,

> [s]ince at least the recombinant AAV containing a therapeutic gene (including recombinant AAV in which **the entire coding regions of Rep and Cap are replaced by nucleic acids of interest**; see at least col. 3, lines 5–7) and generated by the method of Leblois-Prehaud et al that is able to transfect both dividing and non-dividing **human cells *in vitro, ex vivo or in vivo***; and that **wild-type AAV has a single-stranded DNA genome**; the teachings of Leblois-Prehaud et al meet every limitation of the instant claims.

Id. at 12–13.

Appellant argues, among other things, that Leblois-Prehaud does not disclose a second virus having a therapeutic transgene, as required by independent claims 1 and 8. Appeal Br. 23. Appellant also argues that Leblois-Prehaud does not disclose a "virus which can transduce a human cell '*which is not actively dividing*,'" as required by claim 12. *Id.* at 21.

We agree with Appellant that the Examiner has not shown that Leblois-Prehaud discloses the method or cells defined by the claims on appeal. "[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). "[I]t is not enough that the prior art reference . . . includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention." *Id.*

Here, the Examiner has not pointed to a disclosure in Leblois-Prehaud that includes all of the limitations of any of the independent claims on appeal, arranged as in the claims, with no need to combine different teachings within the reference. Claim 1 is directed to a method that requires transducing a mammalian cell with "a recombinant baculovirus comprising a transfer construct comprising a packaging genome of a second virus along with a therapeutic transgene." The Examiner has identified the disclosure in Leblois-Prehaud of a recombinant baculovirus that provides complementary functions for a defective viral genome in a host cell (Final Action 11), and the disclosure of genes that could potentially be used therapeutically (*id.* at 12). However, the Examiner has not identified a disclosure in Leblois-Prehaud of transducing a mammalian cell with a specific recombinant baculovirus that includes all of the elements recited in claim 1, culturing the transduced cell, and harvesting a second virus having the therapeutic transgene, as required by the claim. The Examiner therefore has not shown that Leblois-Prehaud anticipates claim 1 or its dependent claims.

The Examiner relies on the adeno-associated virus (AAV) disclosed by Leblois-Prehaud as the "virus which in its wild state has a single stranded genome" recited in claim 8 and the virus "able to transfect a human cell which is not actively dividing" recited in claim 12. Final Action 12–13. The Examiner has not, however, pointed to a specific description in Leblois-Prehaud of a mammalian cell transduced by a recombinant baculovirus having a nucleic acid sequence coding for a replication-deficient AAV having a therapeutic transgene, as would be required to meet all of the limitations of claim 8. Nor has the Examiner pointed to a specific description

in Leblois-Prehaud of a mammalian cell transduced with a recombinant baculovirus, where the mammalian producer cell produces an AAV vector, as would be required to meet all of the limitations of claim 12. We therefore reverse the rejection of independent claims 8 and 12, and the claims that depend from them, as anticipated by Leblois-Prehaud.

In summary, the Examiner has not persuasively shown that Leblois-Prehaud identically discloses, without any need for picking and choosing, a method or a cell that meets all of the limitations of the claims on appeal. *See Gechter v. Davidson*, 116 F.3d 1454, 1457 (Fed. Cir. 1997) ("Under 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim."). The rejection under 35 U.S.C. § 102(b) based on Leblois-Prehaud is therefore reversed.

Anticipation by Schauber

Claims 15–17 stand rejected as anticipated by Schauber. Claim 15 is representative of the rejected claims. As noted above in the discussion of claim definiteness, the Examiner and Appellant agree that the recitation in claim 15 of "[o]btaining the viral vector of Claim 12" refers to "any viral vector that is produced/generated from a mammalian producer cell transduced with a recombinant baculovirus encoding necessary components/elements for said viral vector." Final Action 8–9; Reply Br. 5. Thus, claim 15 requires obtaining a viral vector as recited in claim 12—i.e., one that (a) is able to transfect a human cell which is not actively dividing, and (b) is substantially free of insect cell membrane—and transducing a human patient's cells with said viral vector.

> The Examiner finds that Schauber teaches
>
> **a lentiviral packaging system** . . . comprising at least: (i) a first vector comprising **a gag, a pol, or gag and pol genes**; (ii) a second vector comprising a functionally modified or **heterologous envelope gene** . . . ; and (iii) a third vector comprising a **rev gene**; and a producer cell comprising the packaging system and **a lentiviral transfer vector** comprising a transgene.

Final Action 18. The Examiner finds that Schauber teaches that "**packaging or producer cells include human cells or cell lines known in the art**." *Id.* at 18–19. Finally, the Examiner finds that Schauber teaches that the transgene in its system can be a therapeutic gene, which can be delivered in vivo or ex vivo to human cells. *Id.* at 19.

The Examiner concludes that the viral vector taught by Schauber meets the limitations of the vector in claim 12 because it "is able to transfect both dividing and non-dividing human cells and is free of insect cell membrane (no insect cell is utilized in the production of the recombinant lentiviral vector)." *Id.* "Therefore, **methods for delivering a transgene, including a therapeutic transgene, to a cell *in vivo or ex vivo*** using the same recombinant lentiviral vector **to treat humans** as taught by Schauber et al have the same method steps and starting materials as those of" claim 15. *Id.*.

We agree with the Examiner that Schauber anticipates claim 15. Schauber discloses a retroviral packaging system and "a producer cell that comprises the packaging system of the invention and a retroviral transfer vector comprising a transgene." Schauber 3:5–6, 22–24. In a working example, Schauber states that "[t]he VSV-G and baculovirus (AcNPV) gp64 envelope genes were subcloned into a mammalian expression vector" and

used for "[l]arge-scale production of pseudotyped vectors . . . as follows: low passage 293T cells were expanded and seeded at 5.75 x 10^8 cells per cell factory." *Id.* at 27:39–40; 28:16–20. 293T cells are human embryonic kidney cells. *Id.* at 4:37–38. Thus, Schauber describes production of viral vectors using mammalian producer cells, which would necessarily be free of insect cell membrane.

In the same example, Schauber states that "pseudotyped HIV vector particles were prepared and tested for their ability to transduce three human cell lines." *Id.* at 29:10–13. "The results . . . demonstrate[d] that gp64-pseudotyped vector was infectious on all three cell lines." *Id.* at 29:21–22. Schauber thus discloses that its vectors are able to transfect human cells, and HIV is a lentivirus that can transduce non-dividing cells. *See* Spec. 1:6–8: "Lentiviruses, such as Human Immunodeficiency Virus I, are promising tools for gene therapy due to their ability to transduce and integrate into the genome of both dividing and non-dividing cells."

The viral vectors disclosed by Schauber meet all of the limitations of the viral vectors required by claim 15, and Schauber discloses transducing human cells with its viral vectors. Although claim 15 recites "[t]ransducing a human patient's cells with said viral vector," the broadest reasonable interpretation of "a human patient" encompasses any human and therefore "a human patient's cells" encompasses human cells generally. We therefore find that Schauber anticipates claim 15.

Appellant argues:

> Claim 12 requires a mammalian cell transduced with a recombinant baculovirus. . . . [C]laims 15–17 depend from claim 12. Claims 15–17 thus each require a mammalian cell

> transduced with a recombinant baculovirus. The Examiner has already found that Schauber does not teach this. *See Office Action* (March 2018) at 20:1–4. Schauber therefore cannot anticipate claims 15–17.

Appeal Br. 25–26.

This argument is unpersuasive because, as discussed above, the step of "[o]btaining the viral vector of Claim 12," as recited in claim 15, simply requires obtaining a viral vector having the properties recited in claim 12. The mammalian producer cell, which is defined in claim 12 based on its production of the same vector, plays no part in the method of claim 15 and is therefore irrelevant to the steps of that method. Appellant in fact agreed with the Examiner's interpretation of the "obtaining" claim limitation as merely requiring "any viral vector that is *produced/generated from* a mammalian producer cell transduced with a recombinant baculovirus encoding necessary components/elements for said viral vector." Final Action 8–9 (emphasis added); Reply Br. 5

In summary, Schauber discloses a method meeting all of the limitations of claim 15. We affirm the rejection of claim 15 under 35 U.S.C. § 102(b) based on Schauber. Claims 16 and 17 fall with claim 15. 37 C.F.R. § 41.37(c)(1)(iv).

Obviousness

Claims 1–17 stand rejected as obvious based on Schauber, Leblois-Prehaud, and Kingsman. The Examiner relies on Schauber for the teachings discussed above. Final Action 20–21. The Examiner finds that Schauber does not teach "each of **a lentivirus transfer construct, *gag*, *pol*, an envelope protein and *rev* being cloned into different baculoviruses** and

transducing a **mammalian producer cell** for generating a recombinant replication-deficient lentivirus particle comprising a therapeutic transgene." *Id.* at 21.

The Examiner finds that Leblois-Prehaud teaches a method for producing recombinant viruses "**based on the use of one or more baculoviruses for providing the complementary functions (e.g., gag, pol and/or env for the retrovirus** . . .**) for the defective recombinant genome in competent host cells**," including mammalian (293) host cells. *Id.* at 21–22. The Examiner also finds that Leblois-Prehaud suggests therapeutic transgenes. *Id.* at 22–23. The Examiner finds that "Kingsman also taught at least the production of retroviral particles, including HIV particles, in a baculovirus expression system (see at least the abstract). Kingsman taught specifically **expression of HIV gag-pol, VSV-G and an HIV-based vector genome in a baculovirus expression system**." *Id.* at 23.

> The Examiner concludes that it would have been obvious
>
> to modify a lentiviral vector production method of Schauber et al by also **at least** cloning Gag/Pol, Rev, VSVG and a lentivirus transfer construct into at least 4 separate baculoviruses and introducing the recombinant baculoviruses into a producer cell such as 293T cells to generate a recombinant replication-deficient lentivirus particle comprising a therapeutic transgene, in light of the teachings of Leblois-Prehaud et al and Kingsman.

Id.

We reverse this rejection with respect to claims 1–11. "An examiner bears the initial burden of presenting a prima facie case of obviousness." *In re Huai-Hung Kao*, 639 F.3d 1057, 1066 (Fed. Cir. 2011). The test of obviousness is "whether the teachings of the prior art, taken as a whole,

would have made obvious the claimed invention." *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991).

Here, we conclude that the Examiner has not persuasively shown that the cited references would have made obvious the inventions defined by the independent claims on appeal. Claim 1 requires, among other things, "a recombinant baculovirus comprising a transfer construct comprising a packaging genome of a second virus." Claim 1. As discussed above in the context of indefiniteness, the meaning of a "packaging genome" is unclear from the record. The Examiner suggests that it might mean "a genome of a second virus to be packaged in the mammalian producer" (Final Action 7) or "**a genome of a second virus that is already packaged (packaging genome)**" (*id.* at 3–4). Appellant argues that a packaging genome is "a *genome* (set of genes) coding for the various polypeptides required to *package* the virus." Appeal Br. 4.

However, the record lacks a definition of "packaging genome" or evidence showing that those skilled in the art recognize a definite meaning for the term. Because it is unclear what structure is required by the claim language, we are unable to determine whether the cited references would have made obvious an invention encompassed by claim 1, and dependent claims 2–7. We therefore reverse the rejection of claims 1–7 under 35 U.S.C. § 103(a). *See In re Steele*, 305 F.2d 859, 862 (CCPA 1962).

Independent claim 8 requires, among other things, a recombinant baculovirus having a nucleic acid sequence "obtained from a virus which in its wild state has a single stranded genome, said second virus being

replication-deficient." Claim 8. The Examiner concludes that it would have been obvious, based on Schauber, Leblois-Prehaud, and Kingsman, to

> clon[e] Gag/Pol, Rev, VSVG and a lentivirus transfer construct into at least 4 separate baculoviruses and introducing the recombinant baculoviruses into a producer cell such as 293T cells to generate a recombinant replication-deficient lentivirus particle comprising a therapeutic transgene.

Final Action 23. The Examiner's explanation of the rejection, however, fails to address how the cited references would have made obvious the "single stranded genome" and "replication-deficient" limitations of claim 8. We therefore reverse the rejection of claim 8, and dependent claims 9–11, under 35 U.S.C. § 103(a).

We affirm the § 103(a) rejection with respect to claims 12–17. Claim 12 is directed to a "mammalian producer cell transduced with a recombinant baculovirus, said mammalian producer cell producing viral vector able to transfect a human cell which is not actively dividing, said viral vector produced by a said mammalian producer cell being substantially free of insect cell membrane." Claim 12.

As discussed above with regard to the anticipation rejection of claims 15–17, Schauber teaches the production of lentiviral (HIV) vectors in 293T (human embryonic kidney) cells. Schauber 28:16–20; 4:37–38. Schauber also discloses that its pseudotyped HIV vector particles were able to transduce human cells. *Id.* at 29:10–13, 21–22. And HIV is an example of a virus that is able to transfect cells that are not actively dividing. Spec. 1:6–8. However, Schauber does not disclose mammalian producer cells, transduced with a recombinant *baculovirus*, that produce the viral vectors, as claimed.

Leblois-Prehaud teaches a system for producing recombinant viral vectors. Leblois-Prehaud 1:6–11. "The system of the invention is based on the use of a baculovirus to provide the complementation functions." *Id.* at 4:54–56. For example, "[t]he baculovirus may also comprise the gag, pol and/or env regions of a retrovirus. A baculo-gag/pol/env thus makes it possible to complement, in a line of competent cells, a retroviral genome lacking any coding viral sequence." *Id.* at 7:32–35.

Leblois-Prehaud teaches that "it was possible, with a recombinant baculovirus, to infect cells of human origin such as immortalized embryonic cells . . . [with] a very high transduction efficiency." *Id.* at 5:55–59. Leblois-Prehaud discloses that its baculovirus-based system has several advantages: (a) "since the baculovirus does not replicate in human cells, the viral preparation obtained is not contaminated by the baculovirus" (*id.* at 5:28–30); (b) "the baculovirus constitutes an inert vector which can be advantageously used for the transfer and expression of virus complementation functions into mammalian, particularly human, cells" (*id.* at 5:63–66); (c) "the large cloning capacity" of baculovirus (*id.* at 6:1); and (d) "the advanced development of the technology of the baculovirus" (*id.* at 6:2–3).

We agree with the Examiner that it would have been obvious to a person of ordinary skill in the art to modify Schauber's retroviral packaging system to use the baculovirus vectors taught by Leblois-Prehaud to express the retroviral complementation functions (e.g., *gag*, *pol*, and an envelope protein) in a mammalian producer cell (e.g., immortalized human embryonic cells). Leblois-Prehaud provides sufficient reason to combine its teachings

with Schauber's, because Leblois-Prehaud teaches that its baculovirus-based system has the advantage of allowing expression of virus complementation functions in human cells without baculovirus contamination of the resulting viral preparation, as well as the large cloning capacity of baculoviral vectors and the advanced state of baculovirus technology.

Appellant argues that Leblois-Prehaud is non-enabled because it "recommends using fibroblast, A549 and HepG2 producer cells. But those cell lines don't work." Appeal Br. 27, citing Airenne Decl.[7] ¶ 6. Dr. Airenne states:

> Carbonell (1987) teaches that baculovirus can penetrate mammalian fibroblast cells and human A549 lung carcinoma cells, yet is not able to transduce (evoke transgene expression in) such cells. Our own unpublished development work similarly shows baculovirus is not able to transduce HepG2 cells for the purpose in the patent (simultaneous transduction with very high MOI and/or several viruses).

Airenne Decl. ¶ 6.

Even assuming that fibroblast, A549, and HepG2 cells would not work in Leblois-Prehaud's baculovirus-based system, however, Appellant's argument fails because Leblois-Prehaud suggests a variety of other cell types. Leblois-Prehaud states:

> Advantageously, the cells used are hepatic, muscular, fibroblastic, embryonic, nerve, epithelial (pulmonary) or ocular (retinal) cells. *There may be mentioned, by way of nonlimiting example, the cells 293* or any derived cell comprising an additional complementation function (293E4, 293E2a, and the like), the A549 cells, the HuH7 cells, the Hep3B cells, the

[7] Declaration under 37 C.F.R. § 1.132 of Kari Airenne, filed Oct. 3, 2017.

> HepG2 cells, the human retinoblastic cells (HER, 911), the HeLa cells, the 3T3 cells or the KB cells.

Leblois-Prehaud 16:15–21 (emphasis added). Thus, Leblois-Prehaud specifically suggests using the 293 cells that are also used by Schauber (*see* Schauber 28:16–20), and Appellant has presented no evidence, or even argued, that 293 cells would not be suitable host cells for use in Leblois-Prehaud's system.

Appellant also argues that Leblois-Prehaud is non-enabling because "baculovirus cannot infect human cells." Appeal Br. 27, citing Airenne Decl. ¶ 4. Dr. Airenne states: "Baculovirus cannot infect mammalian cells. This was true on the critical date. This remains true today." Airenne Decl. ¶ 4.

This argument is unpersuasive. Appellant's argument appears to be based on their definition of "infection" as requiring viral replication in the host cell. Appellant states that "[i]nfection requires the virus replicate in the host cell, forming progeny which then spread to neighboring cells. . . . Baculovirus cannot replicate in human cells." Appeal Br. 9, footnote 5. Leblois-Prehaud, however, relies on a different definition of "infection," because it expressly states that one of "the advantages of the system of the invention" is that "since the *baculovirus does not replicate in human cells*, the viral preparation obtained is not contaminated by the baculovirus." Leblois-Prehaud 5:23–30 (emphasis added).

Thus, when Leblois-Prehaud states that "the applicant has shown that it was possible, with a recombinant baculovirus, to infect cells of human origin such as immortalized embryonic cells" (*id.* at 5:55–57), it is not using "infect" to indicate viral replication. Rather, Leblois-Prehaud characterizes

baculovirus as "an inert vector" useful for "transfer and expression" of virus complementation functions in human cells. *Id.* at 5:63–66.

Appellant also argues that Leblois-Prehaud "admonishes to avoid Schauber's *gag*, *pol* and *env*. Leblois says, 'In the recombinant vectors derived from retroviruses, the *gag*, *pol* and *env* genes are generally deleted.'" Appeal Br. 28, citing Leblois-Prehaud 3:8–9.

This argument is unpersuasive. The section quoted by Appellant refers to retroviral vectors that contain a transgene. The full sentence reads: "In the recombinant vectors derived from retroviruses, the gag, pol and env genes are generally deleted, completely or in part, and replaced by a heterologous nucleic acid sequence of interest." Leblois-Prehaud 3:8–11. Leblois-Prehaud also states that, because the recombinant vectors lack gag, pol, and env, "the production of these various recombinant viruses involves the possibility of transcomplementing the functions deleted from the genome." *Id.* at 16–19. Leblois-Prehaud states that, in its system, "[t]he baculovirus may also comprise the gag, pol and/or env regions of a retrovirus. A baculo-gag/pol/env thus makes it possible to complement, in a line of competent cells, a retroviral genome lacking any coding viral sequence." *Id.* at 7:32–35. Thus, Leblois-Prehaud also requires production of gag, pol, and env to generate retroviral vectors.

Appellant argues that Leblois-Prehaud "also warns that Schauber's 293 encapsidation cells 'hardly make it possible to avoid the production of replicative contaminant viruses.'" Appeal Br. 28, citing Leblois-Prehaud 4:9–10. Similarly, Appellant argues that Leblois-Prehaud "complains Schauber's cell lines 'do not allow . . . in a satisfactory manner for an

industrial use, very highly defective viral genomes'"; "warns that Schauber's encapsidation lines are 'difficult, expensive and restrictive at the industrial level to construct and to validate'"; and "complains that Schauber's cell lines do not enable one to 'obtain very high recombinant retrovirus titres.'" Appeal Br. 28–29, citing Leblois-Prehaud 4:11–15, 5–7, 30–32.

These arguments are unpersuasive, because Leblois-Prehaud does not refer to Schauber's 293 cell line in the relevant discussion. Leblois-Prehaud states:

> Various lines have also been described for the production of defective retroviruses, generally capable of expressing the gag, pol and env genes. Such lines are, for example, the PA317 line (U.S. Pat. No. 4,861,719), the PsiCRIP line (WO90/02806), the GP+envAm-12 line (WO89/07150), the BOSC line (WO94/19478) and the like.

Leblois-Prehaud 3:59–64. Leblois-Prehaud does not cite Schauber's U.S. Patent No. 6,863,884, and Appellant has not provided a persuasive basis for concluding that Leblois-Prehaud's discussion in the cited passages pertained to Schauber as well as the specifically cited lines.

In addition, the discussion cited by Appellant refers to drawbacks of prior art systems, not Leblois-Prehaud's baculovirus-based system. Leblois-Prehaud expressly states that its baculovirus system "makes it possible to overcome these disadvantages." Leblois-Prehaud 4:52–54. Thus, if a skilled artisan would have read the cited disadvantages as applying to Schauber's system, they would have provided further reason to modify Schauber's system by using Leblois-Prehaud's baculovirus-based system.

Appellant argues that "Leblois requires VSV-G. Schauber at 1:61–63 warns that Leblois' VSV-G is cytotoxic to producer cells, thus lowering producer cell yield." Appeal Br. 29.

This argument is unpersuasive for several reasons. First, Appellant points to no basis for the position that Leblois-Prehaud requires using VSV-G. Leblois-Prehaud states that its baculovirus "may also comprise the gag, pol and/or env regions of a retrovirus" (Leblois-Prehaud 7:32–33) and therefore suggests an envelope protein in general, rather than VSV-G specifically. Second, Schauber discloses that the problem referred to in the passage cited by Appellant can be solved by expressing VSV-G under the control of a repressible or inducible promoter. Schauber 1:65 to 2:5. Finally, Schauber's invention involves "pseudotyping of retroviruses with baculoviral envelope proteins," which "provides an alternative to pseudotyping retroviruses with VSV-G." *Id.* at 3:1–4. Thus, combining the components of Schauber's retroviral packaging system with Leblois-Prehaud's baculovirus vectors avoids the known drawback of using VSV-G.

For the reasons discussed above, we affirm the rejection of claim 12 under 35 U.S.C. § 103(a) based on Schauber, Leblois-Prehaud, and Kingsman. Claims 13–17 fall with claim 12 because they were not argued separately. 37 C.F.R. § 41.37(c)(1)(iv).

Provisional Obviousness-type Double Patenting

Claims 1–14 stand provisionally rejected based on obviousness-type double patenting based on claims 1–7 and 10 of application 12/522,646. Final Action 35–36. Appellant does not present any arguments regarding the provisional double patenting rejection in the Appeal Brief or Reply Brief.

We therefore affirm it. *See* 37 C.F.R. § 41.37(c)(1)(iv) (The Appeal Brief must contain "[t]he arguments of appellant with respect to each ground of rejection."); MPEP § 1205.02 (9th Ed., Rev. 08.2017 (Jan. 2018)) ("If a ground of rejection stated by the examiner is not addressed in the appellant's brief, appellant has waived any challenge to that ground of rejection and the Board may summarily sustain it.").

DECISION SUMMARY

In summary:

Claims Rejected	**35 U.S.C. §**	**Reference(s)/Basis**	**Affirmed**	**Reversed**
1–7, 11–17	112, second paragraph	Definiteness	1–7, 11	12–17
1–8, 163-9-2–17	112, first paragraph	Written Description	1–8, 12–17	
9, 10	112, fourth paragraph	Dependent Form	9, 10	
1–17	102(b)	Leblois-Prehaud		1–17
15–17	102(b)	Schauber	15–17	
1–17	103(a)	Schauber, Leblois-Prehaud, Kingsman	12–17	1–11
1–14		Provisional Obviousness-type Double Patenting	1–14	
Overall Outcome			1–17	

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED