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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HARRY E. GRUBER, DOUGLAS J. JOLLY, AMY H. LIN, CHRISTOPHER R. LOGG, and NORIYUKI KASAHARA

Appeal 2019-000177
Application 14/438,564
Technology Center 1600

Before JEFFERY N. FREDMAN, DEBORAH KATZ, and JOHN E. SCHNEIDER *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellant[1] seeks our review[2], under 35 U.S.C. § 134(a), of the Examiner's decision to reject claims 1–9, 12, 16–18, 20–23, 25–32, 34–38,

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[1] We use the word "Appellant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party-in-interest as Tocagen Inc. (Appeal Br. 2.)

[2] We consider the Final Office Action issued May 4, 2017 ("Final Act."), the Appeal Brief filed April 5, 2018 ("Appeal Br."), the Examiner's Answer issued on August 8, 2018 ("Ans."), and the Reply Brief filed October 8, 2018 ("Reply Br.").

51, and 52.[3] (App. Br. 1.) We have jurisdiction under 35 U.S.C. § 6(b). We REVERSE and enter a NEW GROUND OF REJECTION.

Appellant's specification is directed to retroviral vectors for delivering heterologous nucleic acids to cells in gene therapy. (*See* Spec. ¶ 2.)

Appellant's claim 1 recites:

> A recombinant replication competent gammaretrovirus comprising:
> a retroviral GAG protein;
> a retroviral POL protein;
> a retroviral envelope;
> a retroviral polynucleotide 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, said promoter being suitable for expression in a mammalian cell, a *gag* nucleic acid domain, a *pol* nucleic acid domain and an *env* nucleic acid domain;
> a therapeutic cassette comprising at least one mini-promoter cassette having a mini-promoter that is regulated by an RNA polymerase II, wherein *the mini-promoter is about 70-500 bp in length and operably linked to a heterologous polynucleotide, wherein the therapeutic cassette is positioned 5' to the 3' LTR and 3' to the env nucleic acid domain encoding the retroviral envelope, and wherein when only one mini-promoter cassette is present the heterologous polynucleotide is 1.2kb to 2.0 kb in length*; and
> cis-acting sequences necessary for reverse transcription, packaging and integration in a target cell.

(App. Br. 28 (emphasis added).) Claim 1 recites a gammaretrovirus with several limitations on a "therapeutic cassette" that is positioned 5' to the 3'

[3] The Examiner includes claim 19 in the rejections (*see, e.g.* Ans. 3), but Appellant's listing of claim indicates that claim 19 was canceled (*see* Appeal Br. 30.) Accordingly, we do not include claim 19 in our recitation of the specific rejections.

LTR and 3' to the *env* nucleic acid domain encoding the retroviral envelope. The "therapeutic cassette" of claim 1 must have a "mini-promoter" that is (1) regulated by RNA polymerase II, (2) about 70-500 bp long, (3) operably linked to a heterologous polynucleotide.

35 U.S.C. § 102(b) over Kasahara

The Examiner rejects claims 1, 3, 5–9, 12, 16–18, 20, 26–32, 34, 37 and 38 under 35 U.S.C. § 102(b) as being anticipated by Kasahara.[4] (*See* Ans. 3–4.)

Kasahara teaches a recombinant retrovirus for gene delivery. (*See* Kasahara abstract.) Appellant does not dispute that the recombinant retrovirus taught in Kasahara has many of the elements recited in Appellant's claim 1, including: retroviral GAG, POL, and ENV proteins; LTR sequences at the 5′ and 3′ ends; a 5' promoter suitable for expression in a mammalian cell of the gag, pol, and env nucleic acids; a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence; and cis-acting sequences to express proteins necessary for reverse transcription, packaging, and integration of a heterologous nucleic acid in a target cell. (*See* Kasahara ¶ 9; *see* Ans. 3; *see* Appeal Br. 10.)

Appellant does dispute that the heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence taught in Kasahara is a therapeutic cassette comprising a "minipromoter" as required in claim 1. (*See* Appeal Br. 8–11.) We agree with Appellant. Although Kasahara teaches using a portion of the probasin promoter meeting the size

[4] U.S. Patent Application 2005/0002903 A1, published January 6, 2005.

requirements of claim 1 in a retroviral vector (see Kasahara ¶¶ 131-32), this minimal promoter sequence is not "positioned 5' to the 3' LTR and 3' to the env nucleic acid domain encoding the retroviral envelope," as required in claim 1. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Thus, we agree that claim 1 is not anticipated by Kasahara.

The Examiner cites to Figure 2B of Kasahara to show the positioning of the probasin promoter. (*See* Ans. 12.) Figure 2B of Kasahara is reproduced below.

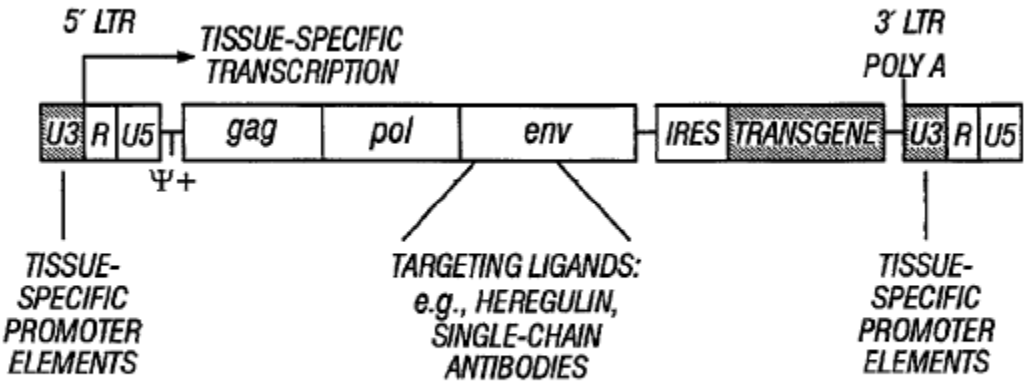


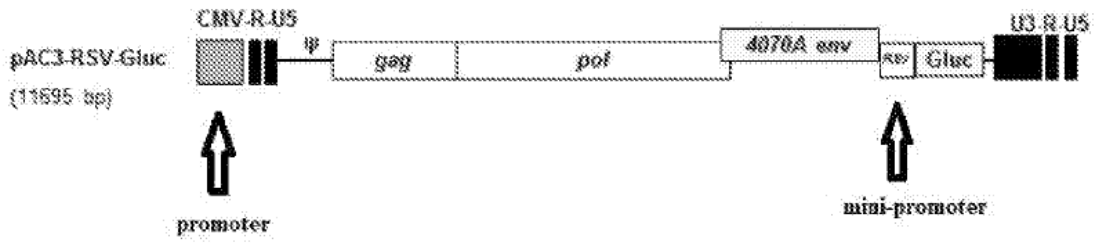
FIG. 2B

Figure 2B depicts IRES (internal ribosome entry site) and transgene sequences located 3′ to the *env* gene sequence and 5′ to the 3′ LTR sequence. Figure 2B depicts other sequences labeled "TISSUE SPECIFIC PROMOTER ELEMENTS" in the 3′ LTR.

Kasahara explains that a "target specific polynucleotide sequence of the retroviral vector can be a tissue-specific promoter sequence, for example

a sequence associated with a growth regulatory gene, such as, for example, probasin." (Kasahara ¶ 9.) Example 6 of Kasahara explains further that "[a] fragment of the rat probasin androgen-sensitive promoter (from -426 to +28) that has been shown to specify prostate-specific gene expression has been engineered into the U3 region of the retroviral 3' LTR in both ecotropic and amphotropic RCR vectors." (Kasahara ¶ 132.) Thus the tissue-specific promoter probasin, is located in the 3′ LTR of the recombinant retrovirus of Kasahara. This element corresponds to the element labeled "TISSUE SPECIFIC PROMOTER ELEMENTS" in Figure 2B, not to the elements labeled "IRES" and "transgene" in Figure 2B.

In comparison, Figure 8B of Appellant's Specification depicts a therapeutic cassette as recited in Appellant's claim 1. (*See* Appeal Br. 10–11.) The portion of Figure 8B highlighted by Appellant is reproduced below.



This portion of Figure 8B depicts an element labeled "RSV," which Appellant has also labeled "mini-promoter" and which is 3′ to the env gene and 5′ to the 3′ LTR.

A comparison of Figure 2B of Kasahara and Figure 8B of Appellant's Specification shows that the tissue-specific probasin promoter taught in Kasahara would not be in the location of the mini-promoter of Figure 8B.

The Examiner acknowledges that Figure 8 of Appellant's Specification differs from Figure 2B of Kasahara, but finds that elsewhere Kasahara teaches heterologous sequences operably linked to a promoter with other examples of integration sites. (*See* Ans. 13, citing Kasahara ¶ 73.) Kasahara teaches

> The heterologous sequence can be linked to a promoter, resulting in a chimeric gene. The heterologous nucleic acid sequence is preferably under control of either the viral LTR promoter-enhancer signals or of an internal promoter, and retained signals within the retroviral LTR can still bring about efficient integration of the vector into the host cell genome. Accordingly, the recombinant retroviral vectors of the invention, the desired sequences, genes and/or gene fragments can be inserted at several sites and under different regulatory sequences.

(Kasahara ¶ 73.) Although this passage suggests control by various regulatory sequences, it does not teach arrangement of a mini-promoter as required in claim 1. We disagree with the Examiner that it supports anticipation of claim 1.

The Examiner also finds that the claim term "minipromoter" encompasses an IRES as taught in Kasahara because an IRES sequence includes minimal elements necessary for translation of an operably linked coding sequence. (*See* Ans. 12.) We are not persuaded that an IRES sequence, which acts provides for initiation of translation from an internal ribosome binding site, falls within the definition of "mini-promoter" being "a regulatory domain that promotes transcription of an operably linked gene or coding nucleic acid sequence" provided in Appellant's Specification. (Spec. ¶ 41, *see also id.* at ¶ 4.)

Because the Examiner fails to show that Kasahara teaches the limitations of a "therapeutic cassette" as recited in claim 1, we reverse the rejection of claim 1 and the claims that depend on it.

35 U.S.C. § 102(e) over Gruber

The Examiner rejects claims 1–9, 12, 16–18, 20, 23, 25–32, 34–38, 51, and 52 under 35 U.S.C. § 102(e) as being anticipated by Gruber.[5] (*See* Ans. 4–6.)

The Examiner asserts that Gruber teaches a therapeutic cassette comprising a mini-promoter cassette operably linked to a heterologous polynucleotide and positioned 5′ to the 3′ LTR and 3′ to the env nucleic acid. (*See* Ans. 5, citing Gruber 1:32–45.) The Examiner finds that Gruber teaches a CMV promoter of 582 nucleotides, as well as an RSV promoter and a CMV-R-U5 promoter. (*See* Ans. 5, citing Gruber 1:61–66, 2:1–5, and 24:46.)

Appellant's arguments against the rejection over Gruber are similar to those against the rejection over Kasahara. Appellant argues that Gruber does not teach a "therapeutic cassette" meeting the requirements recited in claim 1. (*See* Appeal Br. 13–15.) Specifically, Appellant argues that although Gruber teaches a recombinant retrovirus comprising GAG, POL, and ENV proteins and LTRs, it teaches that the retrovirus includes a cassette comprising an IRES operably linked to a heterologous polynucleotide, instead of a minipromoter. (*See* Appeal Br. 14.) Appellant asserts, and we agree, that an IRES nucleotide is not a promoter sequence.

[5] U.S. patent 8,829,173 B2, issued September 9, 2014.

Appellant argues further that the teachings in Gruber of RNA polymerase II promoters, such as the CMV promoter, do not meet the requirements of Appellant's claims because these promoters are located in the LTRs, not in a therapeutic cassette as claimed. Appellant cites Figures 1A and 3 of Gruber in support, arguing that the 582 nucleotides of the CMV promoter are in the LTR, not downstream of the *env* gene and upstream of the 3′ LTR as required in claim 1. (*See* Appeal Br. 15.) Figure 3A of Gruber is reproduced below.

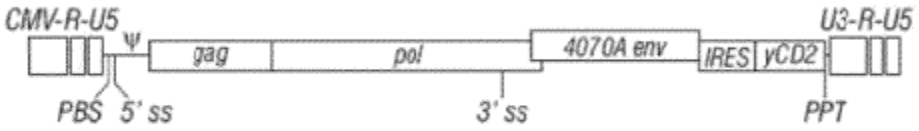


FIG. 3A

Figure 3A provides a schematic drawing of a retrovirus genome, including the notation "CMV" in the R-U5 element. We agree with Appellant that the CMV element is not 3′ to the *env* gene in Figure 3A. Although Gruber teaches heterologous sequences that can include promoter elements (*see* Gruber 24:24–30; *see* Ans. 7), Gruber does not teach that such "cassettes" are positioned between the *env* gene and the 3′ LTR.

Accordingly, we agree with Appellant that Gruber does not anticipate claim 1 or the claims that depend on it.

The Examiner's rejection for anticipation by Gruber includes Appellant's independent claim 51. (*See* Ans. 4.) Claim 51 recites "a therapeutic cassette comprising a mini-promoter cassette operably linked to a heterologous polynucleotide and a miRNA cassette comprising a polIII promoter linked to a primary precursor miRNA (pri-miRNA) for an miRNA or siRNA sequence . . . ." (Appeal Br. 34.)

Although the Examiner finds that Gruber teaches a polIII promoter (*see* Ans. 6 and 15, citing Gruber 17:30–36[6]), we agree with Appellant that the Examiner fails to show that Gruber teaches a therapeutic cassette with two promoters, specifically with a mini-promoter and a polIII promoter that are arranged together in a therapeutic cassette. (*See* Appeal Br. 15.)

Because the Examiner fails to show that Gruber teaches each and every claim of either claim 1 or claim 51, we reverse the rejection of these claims and the claims that depend on them.

Obviousness-type double-patenting

The Examiner made the following rejections under the doctrine of obviousness-type double-patenting:

claims 1–9, 12, 16–18, 20–23, 25–32, 34–38, 51, and 52 over claims 1–29 of patent 8,829,173 (*see* Ans. 7);

claims 1–9, 12, 16–18, 20–23, 25–32, 37, and 38 over claims 1–13 of patent 8,652,460 (*see id.*at 7–8);

claims 1–9, 12, 16–18, 20–23, 25–32, 37, and 38 over claim 21, 23–25, and 51–61 of application 13/882,487, which issued as patent 9,669,049 (*see id.* at 8–9);

claims 1–9, 12, 16–18, 20–23, 25–32, 37, and 38 over claims 1–3, and 7–23 of application 14/274,556, which issued as patent 10,035,983 (*see id.* at 8–9);

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[6] Although the Examiner cites to column 17 of Gruber for a teaching of the polIII promoter, polIII is not mentioned there. Instead, column 18, lines 49–52 of Gruber refer to polIII, reciting: "[a]lternatively polIII transcription units can be inserted in the viral genome with the appropriate siRNA or miRNA's, typically downstream of the 3' envelope gene."

claims 1–9, 12, 16–18, 20–23, 25–32, 37, and 38 over claims 1–8, 12–22, 27–29, 37, 38, and 54–57, and 61–64 of application 14/477,741 which issued as claims 1–13 of patent 9,732,326 (*see id.* at 9).[7]

For each of these rejections, the Examiner states that "[a]lthough the claims at issue are not identical, they are not patentably distinct from each other because the claimed retrovirus comprises elements that overlaps in scope" with the recited patent or application. (*See, e.g.,* Ans. 7.) The Examiner relies on reasoning similar to that asserted for the rejections under 35 U.S.C. § 102(b) and (e). (*See* Ans. 15–22.) For example, the Examiner cites to the descriptions of the probasin promoter and IRES sequences in the specification of patent 8,652,460 in an argument that the patent claims recite a therapeutic cassette with a mini-promoter as Appellant currently claims. (Ans. 17.)

For the reasons provided above, we are not persuaded that Appellant's claims are obvious over the claims of any of the recited patents or applications because the recited patents and applications have not been shown to teach or suggest a therapeutic cassette with the limitations recited in independent claims 1 or 51. Accordingly, we reverse the Examiner's rejections under the doctrine of obviousness-type double-patenting.

New Ground of Rejection

Appellant does not dispute that both Kasahara and Gruber teach recombinant retroviruses comprising many of the elements recited in claim

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[7] The Examiner also rejected Appellant's claims 1–9, 12, 16–23, 25–32, 37, and 38 over the claims of applications 13/638,490 and 15/016,201, but these applications have been abandoned. (*See* Ans. 8 and 9.)

1, including: GAG, POL, and ENV proteins; LTR sequences at the 5′ and 3′ ends; a 5' promoter suitable for expression in a mammalian cell of the gag; pol, and env nucleic acids; a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence; and cis-acting sequences to express proteins necessary for reverse transcription, packaging, and integration of a heterologous nucleic acid in a target cell. (*See* Kasahara ¶ 9; *see* Gruber 1:32–48.)

Both Kasahara and Gruber teach a "transgene cassette" that is located 3' to the env gene sequencer and 5' to the 3' LTR. (*See* Kasahara ¶ 115, Fig. 2; *see* Gruber 1:40–44, Fig. 3A.) Although these cassettes, as a whole, are positioned as required in claim 1, neither Kasahara nor Gruber teaches a therapeutic cassette as recited in claim 1 because both teach regulation of the transgene by an IRES sequence, not a "mini-promoter" about 70-500 bp in length.

According to the specification of both Kasahara and Gruber, IRES sequences are a type of regulatory nucleic acid sequences that provide for the replication, transcription and translation of a coding sequence in a recipient cell. (*See* Kasahara ¶ 71; *see* Gruber 20:66–21:16.) Thus, the IRES sequences taught in Kasahara and Gruber promote the expression of the heterologous gene in the therapeutic cassette of claim 1.

Other means of promoting expression of a heterologous gene expression were known in the art as of Appellant's filing date. For example,

Zhao-Emonet[8] demonstrates that mini-promoters were known in the field of retroviral gene therapy. Specifically, Zhao-Emonet teaches that gene therapy vectors "can be designed by placing a gene of therapeutic interest under the control of tissue-specific transcriptional elements." (Zhao-Emonet abstract.) More specifically, Zhao-Emonet teaches using a 190 bp human minimal CD4 promoter in a Mo-MLV retroviral construct to drive expression of EGFP. (*See* Zhao-Emonet 417.) This promoter falls within the limitations of a mini-promoter as recited in Appellant's claim 1.

Those of ordinary skill in the art would have had a reason to use a mini-promoter as taught in Zhao-Emonet in the retroviruses of Kasahara and Gruber instead of the IRES sequences because Papadakis[9] teaches that "gene therapy applications would . . . benefit from the specific optimisation of 'tailormade' expression cassettes to optimise their therapeutic efficacy." (Papadakis abstract.) Papadakis teaches further that "vector expression cassettes to add further tissue selectivity (transcriptional targeting), may yield significant advantages in gene therapy and serve to minimise the input titer required to evoke a phenotypic response *in vivo*." (Papadakis 89.) Because one of ordinary skill would have had a reasonable expectation of success in making a retroviral vector with mini-promoter regulatory sequences to a recombinant retroviral vector in the position of the IRES sequences taught in Kasahara and Gruber using the cloning techniques

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[8] Zhao-Emonet et al., "T Cell-specific expression from MoMLV retroviral vectors containing a CD4 min-promoter/enhancer," Journal of Gene Medicine 2(416–25 (2000).
[9] Papadakis, et al., "Promoters and Control Elements: Designing Expression Cassettes for Gene Therapy," *Current Gene Therapy* 4:89–113 (2004).

described in Zhao-Emonet, it would have been obvious to make the vector recited in Appellant's claim 1. (*See* Zhao-Emonet 417.)

Accordingly, we enter a new ground of rejection of claim 1 under 35 U.S.C. § 103(a) over the combined teachings of Kasahara or Gruber, Zhao-Emonet, and Papadakis.

We limit our consideration to claim 1. We leave it up to the Examiner to consider the remaining claims in light of these references and other prior art. The PTAB serves as a board of review, not a *de novo* examination tribunal. *See* 35 U.S.C. 6(b).

Conclusion

Upon consideration of the record and for the reasons given, we REVERSE the Examiner's rejections.

In summary:

Claims Rejected	**35 U.S.C. §**	**Basis**	**Affirmed**	**Reversed**	**New Ground**
1, 3, 5–9, 12, 16–18, 20, 26–32, 34, 37, 38	102(b)	Kasahara		1, 3, 5–9, 12, 16–20, 26–32, 34, 37, 38	
1–9, 12, 16–18, 20, 23, 25–32, 34–38, 51, 52	102(e)	Gruber		1–9, 12, 16–18, 20, 23, 25–32, 34–38, 51, 52	
1–9, 12, 16–18, 20–23, 25–32,		Obviousness-type Double Patenting over		1–9, 12, 16–18, 20–23, 25–32,	

34–38, 51, 52		claims 1–29 of patent 8,829,173		34–38, 51, 52	
1–9, 12, 16–18, 20–23,, 25–32, 37, 38		Obviousness-type Double Patenting overs claims 1–13 of patent 8,652,460		1–9, 12, 16–18, 20–23, 25–32, 37, 38	
1–9, 12, 16–18, 20–23, 25–32, 37, 38		Obviousness-type Double Patenting over claim 21, 23–25, and 51–61 of application 13/882,487 (issued as patent 9,669,049)		1–9, 12, 16–18, 20–23, 25–32, 37, 38	
1–9, 12, 16–18, 20–23, 25–32, 37, 38		Obviousness-type Double Patenting over claims 1–3, and 7–23 of application 14/274,556, which has issued		1–9, 12, 16–18, 20–23, 25–32, 37, 38	

		as patent 10,035,983[10]			
1–9, 12, 16–18, 20–23, 25–32, 37, 38		Obviousness-type Double Patenting over claims 1–13 of patent 9,732,326		1–9, 12, 16–18, 20–23, 25–32, 37, 38	
1	103(a)	Kasahara or Gruber, Zhoa-Emonet, and Papadakis			1
Overall Outcome				1–9, 12, 16–18, 20–23, 25–32, 34–38, 51, 52	1

This decision includes a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). 37 C.F.R. § 41.50(b) provides that "[a] new ground of rejection ... shall not be considered final for judicial review." 37 C.F.R. § 41.50(b) also provides that the Appellant:

[10] As explained above, we do not reach this rejection per *Ex parte Moncla*, Appeal No. 2009-006448 (PTAB June 22, 2010) (holding that it is premature to address a provisional rejection) (designated precedential).

> WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:
>
> (1) Reopen prosecution. Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner . . . .
>
> (2) Request rehearing. Request that the proceeding be reheard under § 41.52 by the Board upon the same record . . . .

(emphasis added).

REVERSED

37 C.F.R. § 41.50(b)