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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JAMES C. CICCARELLI,
NORIYUKI KASAHARA, and CHRISTOPHER R. LOGG¹

Appeal 2014-009731
Application 13/567,064
Technology Center 1600

Before FRANCISCO C. PRATS, ULRIKE W. JENKS, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134(a) involves claims to methods of making a set of lentivirus vectors that function as negative modulators of an immune response involving the Human Leukocyte Antigens (HLA). The Examiner rejected the claims for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

¹ Appellants state that the “real party in interest is The National Institute of Transplantation Foundation.” App. Br. 2.

STATEMENT OF THE CASE

The sole rejection before us for review is the Examiner's rejection of claims 1, 2, 5, 6, 9–16, and 18–20, under 35 U.S.C. § 103(a), for obviousness over Rossi,² Radcliffe,³ and Uchida.⁴ Final Action 3–5.⁵

Claim 1, the sole independent claim on appeal,⁶ illustrates the appealed subject matter and reads as follows (App. Br. 21):

1. A method of making a kit that comprises a set of lentivirus vectors for altering allogeneic human cells for a human recipient, the method comprising:
 - forming the set of lentivirus vectors wherein each of the lentivirus vectors expresses a sequence targeting a consensus conserved nucleic acid sequence, which when expressed in cells, functions as a negative modulator for nucleic acid encoding a domain having a mismatch in an HLA protein and wherein the set of lentivirus vectors comprises individual lentivirus vectors that correspond to individual HLA mismatches for a set of HLA mismatches that consist of HLA Class I mismatches and at least one HLA Class II mismatch; - wherein the kit is for treatment of human cells by an appropriate subset of the set of lentivirus vectors based on determining a subset of the set of HLA mismatches between a human

² John Rossi et al., US 2005/0227940 A1 (published Oct. 13, 2005).

³ Philippa Radcliffe et al., US 2005/0106559 A1 (published May 19, 2005).

⁴ Nobuko Uchida et al., U.S. Patent No. 5,928,638 (issued Jul. 27, 1999).

⁵ The Final Action also included a rejection under 35 U.S.C. § 112, first paragraph (Final Action 2), and an obviousness rejection under § 103(a) over a different combination of references (*id.* at 7–9). Those rejections have been withdrawn. *See* Advisory Action (entered October 2, 2013); *see also* Ans. 2.

⁶ Appellants contend that claim 16 is an independent claim. App. Br. 14–15. As is evident, however, claim 16 recites “[a] subset of the lentivirus vectors of the kit of claim 1” (*id.* at 23), and, therefore is not an independent claim.

donor and a human recipient or between human cells and a human recipient.

OBVIOUSNESS

The Examiner's Position

The Examiner cited Rossi as describing a process in which one or more expression cassettes encoding an RNAi [interfering RNA] molecule corresponding to a gene encoding a MHC class I gene are introduced into a cell, “wherein the RNAi molecule is expressed and initiates RNA interference of expression of the MHC gene, thereby down-regulating expression of the MHC gene and disrupting antigen presentation (page 15).” Final Action 4. The Examiner noted Rossi’s disclosure that “siRNA [small interfering RNA] can be delivered using a viral vector selected from retroviral and lentiviral vectors (page 8).” *Id.*

The Examiner cited Uchida as disclosing “the routine method steps set forth in instant claims 6–10 and 12–15. For example see columns 1–7 and 16–24.” *Id.* (citing *In re Aller*, 220 F.2d 454, 456 (CCPA 1955) (“Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation.”)).

The Examiner cited Radcliffe for its disclosure of “making a library of lentiviral vectors (claim 59).” Final Action 4.

The Examiner concluded that an ordinary artisan would have considered it prima facie obvious “to combine the teaching of Rossi taken with Uchida et al. and Radcliffe et al., namely to use routine steps for making a composition comprising a set of lentiviral vectors as set forth in claimed invention.” *Id.* at 5.

The Examiner reasoned that an ordinary artisan “would have been motivated to combine the teaching[s] to prepare the composition for deliver[y] to an animal or to determine which dosage unit form is the most effective for reducing expression of an HLA protein.” *Id.* (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007) (“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”)).

The Examiner further reasoned that an ordinary artisan “would have been motivated to make a kit comprising a set of lentiviral vectors to save time from having to make another vector each time a different HLA mismatch is required.” *Id.*

Analysis

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. [The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.

In re Fritch, 972 F.2d 1260, 1265 (Fed. Cir. 1992) (citations and internal quotations omitted, bracketed material in original).

For a number of reasons, we agree with Appellants that the Examiner has not established a prima facie case of obviousness as to Appellants’ claim 1, the sole independent claim on appeal.

As our reviewing court has explained, “section 103 requires a fact-intensive comparison of the claimed process with the prior art rather than the mechanical application of one or another *per se* rule.” *In re Ochiai*, 71 F.3d 1565, 1571 (Fed. Cir. 1995); *see also id.* at 1572 (“[R]eliance on *per se* rules

of obviousness is legally incorrect and must cease.”); *see also KSR*, 550 U.S. at 418 (“[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”).

Among the required findings of fact, the Supreme Court reaffirmed in *KSR* that the “the scope and content of the prior art are to be determined . . . [and] differences between the prior art and the claims at issue are to be ascertained.” *KSR*, 550 U.S. at 406 (quoting *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966)).

As noted above, the Examiner provided a summary of the disclosures in the cited prior art references. The Examiner did not, however, explain specifically which disclosures in the prior art correspond to which features recited in the claims. Nor did the Examiner identify with any degree of particularity the differences between the invention recited in independent claim 1 and the cited prior art. Because the Examiner did not, as required, make specific findings as to the differences between the claims and the prior art, the Examiner did not make clear, specifically, what particular modifications to Rossi’s process must be made to arrive at the process recited in claim 1, and why the prior art would have suggested those modifications.

To that end, although the Supreme Court has emphasized “an expansive and flexible approach” to the obviousness question, *KSR*, 550 U.S. at 415, the Court, nonetheless, also has reaffirmed the importance of determining “whether there was an apparent reason to combine the known

elements *in the fashion claimed* by the patent at issue.” *Id.* at 418 (emphasis added).

Ultimately, therefore, “[i]n determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.” *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted).

In addition to not expressly making the specific findings of fact, discussed above, critical to a conclusion of *prima facie* obviousness, we agree with Appellants that the Examiner has not explained persuasively why the cited references would have suggested the process recited in Appellants’ claim 1.

Claim 1 recites a method of making a kit composed of a set of lentivirus vectors for altering allogeneic human cells for a human recipient. App. Br. 21. Claim 1 requires its practitioner to form a set of lentivirus vectors, with each of the lentivirus vectors expressing a sequence targeting a consensus conserved nucleic acid sequence. *Id.* When present in cells, the expressed sequences must function as negative modulators for nucleic acids encoding a domain having a mismatch in an HLA protein. *Id.*

In particular, claim 1 requires the set/library of vectors to include individual lentivirus vectors that correspond to a set of HLA mismatches that “consist of HLA Class I mismatches and at least one HLA Class II mismatch.” *Id.* As intimated in the last “wherein” clause of claim 1, the kit may be used to address HLA mismatches between a human cell donor and a recipient, by inhibiting the immune response to the mismatched HLA

antigens. *Id.*; *see also* Spec. ¶¶ 4–28 (turning off/inhibiting HLA immune response useful for avoiding graft rejection in variety of tissues).

Turning to the cited prior art, Rossi discloses “a method for amplifying expression of double-stranded RNA, preferably RNAi, in a cell, preferably a mammalian cell. The method comprises generally introducing a plurality of expression cassettes encoding double-stranded RNA, including siRNA or shRNA.” Rossi ¶ 22; *see also id.* at p. 14 (claim 1). Rossi further discloses:

The method preferably comprises introducing the expression vehicles into the cell together as a single unit, and more preferably as a RNAi-expressing concatamer, preferably a siRNA- or shRNA-expressing (collectively si/shRNA [short hairpin RNA]) concatamer, which is more preferably in the form of an expression vector, comprising a plurality of promoter RNAi (si/shRNA) expression cassettes, one or more of which express RNAi (si/shRNA).

Id.

Like the library recited in Appellants’ claim 1, as the Examiner found, Rossi discloses that its vector may be used to down-regulate expression of HLA genes. *Id.* ¶ 32 (“[I]nterfering with expression of MHC class I genes using siRNA homologous with a sequence conserved in most classical polymorphic HLA-A, -B and -C loci offers a mechanism to help prevent rejection of an allogeneic graft or cells that express immunogenic vector-encoded transgenes.”); *see also id.* at p. 15 (claim 13).

Rossi also discloses that its vector can be configured to target multiple HLA genes:

Additional changes can be envisioned to further improve the efficacy of the siRNA vector, such as using enhancer elements, alternative Pol III promoters, alternative promoters,

and a combination of siRNAs directed to different regions of the HLA genes and/or targeting multiple essential components of antigen processing and MHC (class I and II) expression.

Id. ¶ 72 (emphasis added).

The Examiner contends, apparently in view of these teachings, that an ordinary artisan “would have been motivated to make a kit comprising a set of lentiviral vectors to save time from having to make another vector each time a different HLA mismatch is required.” Final Action 5; *see also* Ans. 5–7.

As seen above, however, Rossi discloses configuring its single vector to target multiple HLA mismatches. Rossi ¶ 72. The Examiner does not explain with any degree of particularity how preparing a library of vectors, such as is disclosed in Radcliffe, from which suitable candidates must be chosen, would save time, as compared to Rossi’s use of a single vector that already contains sequences that address multiple potential HLA mismatches.

The Examiner argues instead:

One of ordinary skill in the art would have been motivated to make a library of separate vectors instead of a library of vectors comprising siRNA targeting multiple HLA protein mismatches so one ordinary skill in the art could pick and choose which HLA protein(s) need to be targeted. This is a simple substitution of one known element for another to obtain predictable results or obvious to try choosing from a finite number of identified predictable solutions with a reasonable expectation of success. “Citing KSR, the Board stated that “when there is a motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.” See *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009).

Ans. 4–5; *see also id.* at 6 (“[M]aking a library of vectors containing a siRNA targeting a HLA protein is a simple substitution.”).

As discussed above, however, Rossi discloses that its single vector may be configured to target multiple HLA mismatches. Rossi ¶ 72. The Examiner does not explain with any degree of specificity why either Uchida or Radcliffe suggests that preparing a library containing multiple vectors, from which one must pick and choose suitable elements (as the Examiner argues), would be considered substantially equivalent to simply preparing a vector that contains multiple sequences capable of inhibiting distinct HLA genes, as taught by Rossi.

Indeed, the Examiner does not discuss the teachings in either Radcliffe or Uchida with any degree of specificity. The Examiner, therefore, has not provided adequate evidentiary support for the contention that arriving at the process in Appellants’ claim 1 from the teachings in Rossi amounts to a simple substitution of one known prior art element for another. While we acknowledge Radcliffe’s disclosure of preparing a library of vectors that include modulator genes, selectable markers, and regulatory sequences (*see* Radcliffe p. 81 (claims 48 and 59)), we find the Examiner’s indicated motivation to substitute Radcliffe’s vector library, from which one must pick and choose suitable elements, for Rossi’s single vector that already contains those elements insufficient to establish a *prima facie* case of obviousness.

In sum, for the reasons discussed, we agree with Appellants that the Examiner has not provided a persuasive, specific, fact-based explanation as to why Rossi, Uchida, and Radcliffe would have suggested the process recited in Appellants’ claim 1 to an ordinary artisan. Accordingly, we

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reverse the Examiner's rejection of that claim, and its dependent claims,
over those references.

REVERSED