

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DOUGLAS E. BROUGH, C. RICHTER KING, IMRE KOVESDI
and JASPER J. SCHAIBLE

Appeal 2007-1619
Application 10/424,638
Technology Center 1600

Decided: December 6, 2007

Before, TONI R. SCHEINER, DEMETRA J. MILLS and RICHARD M.
LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 52-60, 62, and 64-88. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The claims are directed to an adenoviral vector comprising a coding sequence for tumor necrosis factor (“TNF”) and the vector’s use to treat a tumor or cancer in a mammal. TNF “is well known for its anti-tumor effects and ability to act synergistically with radiation therapy” (Specification 1).

The rejection of claims 52-60, 62, and 64-88, which are all the pending claims, are on appeal (Appeal Br. 1¹). Appellants seek review of the following rejections:

Claims 52-60, 62, and 64-86 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement (Answer 3); and

Claims 87 and 88 stand rejected under 35 U.S.C. § 103(a) as obvious over Staba (Staba, *Gene Therapy*, 5: 293-300, 1998), Kovesdi (U.S. Pat. No. 5,851,806, Dec. 22, 1998), and Rathjen (EP 0 486 526 B1, May 22, 1996) (Answer 5).

Within each rejection, the claims are argued as a group; separate reasons are not provided for the patentability of any individual claim. We select claims 52, 87, and 88 as representative of the claims for deciding all issues in the appeal. *See* 37 C.F.R. § 41.37(c)(1)(vii). Claims 52, 87, and 88 read as follows:

52. An adenoviral vector comprising:

- (a) an adenoviral genome deficient in the E1, E3, and E4 regions and retaining at least a right side inverted terminal repeat (ITR), an E4 polyadenylation sequence, and an E4 promoter, wherein the adenoviral genome is a serotype-2 genome, a serotype-5 genome, or a mixture thereof,
- (b) a CArG domain of an Egr-1 promoter,
- (c) a nucleic acid sequence coding for TNF- α comprising SEQ ID NO: 2 operably linked to the CArG domain of an Egr-1 promoter,
- (d) a 3' untranslated sequence (UTR),
- (e) a first SV40 polyadenylation sequence, and
- (f) a spacer element comprising a bovine growth hormone polyadenylation sequence, a glucuronidase gene, and

¹ “Appeal Br.” refers to the Corrected Appeal Brief was filed Aug. 22, 2006.

a second SV40 polyadenylation sequence, wherein the E1 region of the adenoviral genome is replaced with elements (b), (c), (d), and (e) in sequence from 5' to 3' relative to the adenoviral genome, and

wherein element (f) is located in the E4 region of the adenoviral genome between the E4 polyadenylation sequence and the E4 promoter.

87. A method of treating a tumor or cancer in a mammal, which method comprises administering a composition comprising

(i) an anti-tumor or anti-cancer effective amount of an adenoviral vector comprising (a) an adenoviral genome deficient in the E4 region of the adenoviral genome, and optionally deficient in the E1 region, the E2 region, and/or the E3 region of the adenoviral genome, (b) a nucleic acid sequence coding for TNF, and (c) a radiation inducible promoter operably linked to the nucleic acid sequence coding for TNF, and

(ii) a TNF antagonist to the tumor or cancer of the mammal.

88. The method of claim 87, wherein the TNF antagonist is at least one TNF antagonist selected from the group consisting of soluble TNF receptors and anti-TNF anti-bodies.

REJECTION UNDER § 112, FIRST PARAGRAPH

Claims 52-60, 62, and 64-86 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Claim 52 is directed to an adenoviral vector which comprises, *inter alia*, “(f) a spacer element comprising a bovine growth hormone polyadenylation sequence, a glucuronidase gene, and a second SV40 polyadenylation sequence.” The “spacer element” with the two non-adenoviral vector polyadenylation sequences (bovine growth hormone and SV40) was added by amendment (*see* Amendment filed Mar. 24, 2005).

The Examiner contends that the Specification does not describe an adenoviral vector having a spacer element comprising two non-adenoviral vector polyadenylation sequences derived from bovine growth hormone and SV40, respectively (Answer 3-4 and 7-8). Appellants contend that the Specification provides written description for the claimed spacer element comprising more than one non-adenoviral polyadenylation sequence (Reply Br. 2²).

Under 35 U.S.C. § 112, first paragraph, the specification must contain a written description of the invention. Thus, when claims are amended during patent prosecution, the claimed invention, in its amended form, must be described in the specification. An applicant complies with the written description requirement ‘by describing the invention, with all its claimed limitations.’ *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, (1997).” *Gentry Gallery v. The Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998).

Appellants argue that support for the presence of two non-adenoviral vector polyadenylation sequences can be found in paragraphs [0029] and [0030] of the Specification (Appeal Br. 4). They rely on the following disclosure to provide written description for the claimed limitation of “a bovine growth hormone polyadenylation sequence . . . and a second SV40 polyadenylation sequence”:

More preferably, the spacer element comprises an additional polyadenylation sequence and/or a foreign gene.
(Specification 7: [0029]).

² “Reply Br.” refers to the Reply Brief filed Dec. 15, 2006.

The spacer element can comprise any suitable polyadenylation sequence. Examples of suitable polyadenylation sequences include synthetic optimized sequences, as well as the polyadenylation sequences of BGH (Bovine Growth Hormone), polyoma virus, TK (Thymidine Kinase), EBV (Epstein Barr Virus), and the papillomaviruses, including human papillomaviruses and BPV (Bovine Papilloma Virus).

(Specification 7: [0030]).

They argue

the term “an” is known by those of ordinary skill in the art to refer to both the singular and plural. Thus, one of ordinary skill in the art would construe the phrase “an additional polyadenylation sequence” [Specification 7: [0029]] as encompassing one, two, three, or more polyadenylation sequences.

(Reply Br. 2).

We recognize that in some circumstances “an” can mean “one or more,” such as when used in a claim with the term “comprising.” *Free Motion Fitness Inc. v. Cybex Int’l Inc.*, 423 F.3d 1343, 1350 (Fed. Cir. 2005); *Tandon Corp. v. United States Int’l Trade Comm’n*, 831 F.2d 1017, 1023 (Fed. Cir. 1987). However, we do not find that this is the case here. In paragraph [0029] of the Specification, it is stated that “the spacer element comprises an additional polyadenylation sequence.” The polyadenylation sequence is “additional” to the native E4 adenoviral polyadenylation sequence in the spacer element (Specification 6: [0027]). Had more than one “additional polyadenylation sequence” been intended, the Specification would have stated that the spacer element comprises additional polyadenylation *sequences*. Instead, the Specification only refers to the polyadenylation sequence in the singular.

Following paragraph [0029], it is stated in paragraph [0030] (*see supra*) that the spacer element “can comprise any suitable polyadenylation sequence” – again using the singular form of the word to characterize the polyadenylation element, rather than the plural. Furthermore, in the examples section of the Specification, Example 1 describes an adenoviral vector with SV40 in the spacer element, but no other non-native adenoviral vector polyadenylation sequence (Specification 16: [0058]). In sum, there is no express description of a vector with two non-native adenoviral vector polyadenylation sequences present in the spacer element.

However, Appellants contend that there is inherent support for adenoviral vectors comprising more than one non-adenoviral vector polyadenylation site (Appeal Br. 4). They assert that “the claimed spacer is an inherent feature of the claimed invention, and is present in the adenoviral vector represented by SEQ ID NO: 1 at nucleotide position 29,960 to position 32,419” (Reply Br. 2).

We do not find this argument persuasive. Appellants do not identify the specific nucleotide positions where each of the polyadenylation sequences can be found. Thus, Appellants have not provided specific evidence that the polyadenylation sequences are, in fact, present in SEQ ID NO: 1. As noted by the Examiner (Answer 9), Example 1, which describes the adenoviral vector having SEQ ID NO: 1, states that the vector comprises the SV40 polyadenylation sequence in its spacer, but does not state that the bovine growth hormone sequence is also present. Thus, the express description of the vector of SEQ ID NO: 1 in the Specification is contrary to Appellants’ assertion that it contains both the SV40 and bovine growth hormone polyadenylation sequences. Appellants have not rebutted this

Specification disclosure by pointing specifically to where the two polyadenylation sequences are situated in SEQ ID NO: 1.

For the foregoing reasons, we are not persuaded by Appellants' arguments or evidence that the Examiner erred in finding that claim 52 lacks written description. The rejection of claim 52 is affirmed. Claims 53-60, 62, and 64-86 fall with claim 52 because separate reasons for their patentability were not provided.

REJECTION UNDER 35 U.S.C. § 103

Claims 87 and 88 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Staba, Kovesdi and Rathjen.

Claim 87 is directed to a "method of treating a tumor or cancer in a mammal" which comprises administering a composition comprising (i) an anti-tumor or anti-cancer adenoviral vector; and (ii) a TNF antagonist. The vector is (a) deficient in the E4 region of the adenoviral genome; and (b) comprises a TNF coding sequence which is operably linked to (c) a radiation inducible promoter. The vector is also (a) "optionally deficient in the E1 region, the E2 region, and/or the E3 region of the adenoviral genome." Claim 88 recites that the TNF antagonist is a soluble TNF receptor or anti-TNF-antibody.

The Examiner finds Staba describes an adenoviral vector to treat a human malignant glioma xenograft ("a tumor") that comprises a TNF coding sequence operably linked to the radiation inducible promoter Egr-1, meeting the limitations of (b) and (c) of claim 87 (Answer 5). However, the Examiner finds that Staba does not describe an adenoviral vector which is deficient in the E4 region or optionally in E1, E2, and/or E3 as defined claim

87, element (a) (Answer 5-6). Staba also does not describe administering its adenoviral vector in combination with a TNF antagonist as recited in claim 87.

To meet the limitations of claim 87 which are not found in Staba, the Examiner relies on Kovesdi and Rathjen. The Examiner finds that Kovesdi describes an adenoviral vector which is deficient in E4 (*see* Kovesdi, at col. 31, ll. 40-43; at col. 8, ll. 25-30) and which may also be deficient in E1, E2, or E3 (*see* Kovesdi, at col. 8, ll. 2-25) (Answer 6). Thus, the Examiner finds that Kovesdi describes an adenoviral vector which satisfies the limitations of element (a) of claim 87 (Answer 6).

For the description of a composition that contains (i) an adenoviral vector and (ii) a TNF antagonist, the Examiner finds that

Rathjen teaches that infusion of a gene encoding TNF into cancer patients has resulted in tumor regression (pages 2, lines 17-20). However, side effects have been observed after the infusion process. Therefore, Rathjen developed TNF antibodies and uses the TNF antibodies for inhibiting undesirable side effects, while tumor regression activity remain in the mammal undergoing cancer therapy using TNF (Answer 6).

The Examiner finds that persons of ordinary skill in the art would have been motivated to have utilized the adenovirus vector of Kovesdi to deliver TNF for its known advantages (Answer 6, 9, and 10). The Examiner also finds that persons of ordinary skill in the art would have been motivated to have utilized anti-TNF antibodies (*see* claim 87, (ii) and claim 88) “in combination with a method of cancer gene therapy comprising an adenoviral vector comprising a nucleic acid encoding TNF . . . because of the known side effects of TNF in a mammal” as taught by Rathjen (Answer 7).

“[T]he Examiner bears the initial burden, on review of the prior art . . . , of presenting a prima facie case of unpatentability.” *In re Oetiker*, 977 F.2d 1443, 1445, (Fed. Cir. 1992). To establish a prima facie case of obviousness, the Examiner must provide evidence that the prior art teaches or suggests all the elements of the claim and a reason that would have prompted persons of ordinary skill in the art to combine the prior art elements to have made the claimed invention. *See KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

After finding all the elements of claims 87 and 88 in the prior art (Answer 6; *see supra*), the Examiner reasons that persons of ordinary skill in the art would have been prompted to have utilized Kovesdi’s adenoviral vector to deliver TNF for its known advantages in expressing foreign genes in cells (*see Answer 9*). To meet the composition of claim 87 comprising an adenoviral vector and a TNF antagonist, the Examiner finds that Rathjen teaches administering an adenoviral vector expressing TNF with an anti-TNF antibody (a TNF antagonist; *see claim 87*) in order to avoid the side-effects association with the clinical use of TNF (*see Answer 7*). We agree with the Examiner’s reasoning, and thus conclude that the Examiner has set forth adequate evidence to establish a prima facie case of unpatentability.

Once prima facie obviousness has been established, burden of coming forward with evidence or argument shifts to the applicant. *See Oetiker*, 977 F.2d at 1445. *See also Hyatt v. Dudas*, 492 F.3d 1365, 1369-70 (Fed. Cir. 2007). Thus, we turn to Appellants’ arguments.

Appellants contend that persons of skill in the art “would not be motivated to depart from the teachings of the Staba reference and modify the disclosure thereof by making further deletions to the adenoviral vector” as

taught by Kovesdi (Appeal Br. 5). They argue that there “is nothing in the Staba reference to suggest that the adenoviral vector disclosed therein was less than optimal for inhibiting tumor growth” (Appeal Br. 6).

We do not agree with Appellants that Staba must describe its adenoviral vector as “less than optimal for inhibiting growth” (*id.*) for persons of ordinary skill in the art to have had reason to have replaced it with Kovesdi’s vector for TNF expression. Kovesdi describes a multiply replication deficient adenoviral vector useful for expressing therapeutic genes (*see* Answer 9; Kovesdi, at col. 5, ll. 45-60). Staba describes expression of the TNF gene using another known adenoviral vector (Answer 5; Staba, Abstract). Thus, both the claimed adenoviral vector and the TNF gene were known. It was also known to use an adenoviral vector to express the known TNF gene.

“[W]hen a patent ‘simply arranges old elements with each performing the same function it had been known to perform’ and yields no more than one would expect from such an arrangement, the combination is obvious.” *KSR*, 117 S.Ct. at 1740 (quoting *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, (1976). “[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious,” the relevant question is “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.*

In this case, Kovesdi’s vector – which meets all the limitations of the adenoviral vector of claim 87 – is employed for its established function in the therapeutic expression of genes. Staba describes TNF as a therapeutic gene. We find that Staba’s teaching that an adenoviral vector is useful for TNF expression in treating tumors would have led persons of ordinary skill

in the art to reasonably expect that other adenoviral vectors would be effective for the same purpose. Therefore, Kovesdi's vector is being employed for its known and expected benefit in expressing a therapeutic gene. Appellants have not provided any evidence that the combination of Kovesdi's vector with Staba's TNF gene achieves results that are anything more than would be expected.

Appellants also argue that

The Rathjen application does not compensate for the deficiencies of the Staba reference, in that it does not disclose adenoviral vectors, and does not provide any reason to administer a TNF antagonist in conjunction with another therapeutic, much less a replication-deficient adenoviral vector. Indeed, the only source of such a disclosure or suggestion is Applicant's own disclosure, the consideration of which is improper

(Appeal Br. 6).

We are not persuaded by this argument that the Examiner erred in finding the claimed invention to have been suggested by Staba, Kovesdi, and Rathjen. Rathjen clearly provides a reason to have combined TNF administration with an anti-TNF antibody: to avoid the deleterious side-effects associated with TNF use (Answer 6; Rathjen, at p. 1). Thus, the Examiner did not rely on Appellants' Specification for the source of the suggestion. The suggestion is explicitly found in the prior art.

For the foregoing reasons, we affirm the rejections of claims 87 and 88.

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TIME PERIOD

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

AFFIRMED

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