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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HARUO SUGIYAMA[1]

Appeal 2015-004953
Application 13/748,984
Technology Center 1600

Before DONALD E. ADAMS, TAWEN CHANG, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to an isolated cytotoxic T-lymphoctye recognizing a complex between particular Wilms' tumor gene 1 ("WT1") peptides and human leukocyte antigen ("HLA") serotype A26, which have been rejected as obvious and as being directed to non-statutory subject matter. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

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[1] Appellants identify the Real Party in Interest as International Institute of Cancer Immunology, Inc. (Appeal Br. 1.)

STATEMENT OF THE CASE

WT1 is expressed in leukemia and various solid cancers. (Spec. ¶ 2.) It has been "demonstrated *in vitro* that, when peripheral blood mononuclear cells positive for HLA-A*0201 or HLA-A*2402 are stimulated with WTl-derived peptides, peptide-specific cytotoxic T-lymphocytes (CTLs) are induced." (*Id.*) Appellant's invention is directed to a CTL recognizing different WT1 peptides and a different HLA serotype. (Spec. ¶ 4.)

Claims 19 and 25 are on appeal. Claim 19 is representative and reads as follows:

> 19. An isolated cytotoxic T-lymphocyte (CTL), which recognizes a complex between a peptide selected from the group consisting of the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 8, and SEQ ID NO: 9 and human leukocyte antigen serotype A26 (HLAA26 antigen).

(Appeal Br. Claims App'x i.)

The following grounds of rejection by the Examiner are before us on review:

Claims 19 and 25 under 35 U.S.C. § 103 as unpatentable over Gaiger[2] and Yashiki.[3]

Claims 19 and 25 under 35 U.S.C. § 101 as being directed to patent ineligible subject matter.

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[2] Gaiger et al., US2003/0082194 A1, published May 1, 2003.
[3] Yashiki et al., *HLA-A*26, HLA-B*4002, HLA-B*4006, and HLA-B*4801 Alleles Predispose to Adult T Cell Leukemia: The Limited Recognition of HTLV Type 1 Tax Peptide Anchor Motifs and Epitopes to Generate Anti-HTLV Type 1 Tax CD8$^+$ Cytotoxic T Lymphocytes*, 17(11) AIDS Research and Human Retroviruses, 1047–1061 (2001).

DISCUSSION

I

Obviousness

The Examiner finds that "Gaiger teaches compositions for eliciting immune and T cell response to Wilms' Tumor antigen polypeptide-derived antigenic fragments." (Final Action 4; Ans. 4.) The Examiner notes that "Gaiger discloses basic methodologies for treating diseases associated with WT1 expression[, one such disease being leukemia,] in a patient comprising incubating CD4+ or CD8+ T cells isolated from the patient with a WT1 polypeptide (or APC expressing a WT1 polypeptide), and then administering to the patient an effective amount of the proliferated T cells." (Final Action 4–5; Ans. 4–5.) The Examiner further finds that peptide fragment SEQ ID NO: 166, which is the same as claimed SEQ ID NO: 9, is disclosed in Gaiger as a WT1 peptide that can be used in the disclosed invention of Gaiger. (Final Action 4; Ans. 4.) According to the Examiner, the foregoing amounts to a disclosure of WT1 peptides, such as SEQ ID NO: 166, being used to create cytotoxic lymphocytes ("CTLs"), which are administered to treat patients with a WT1 disease, such as leukemia. (Final Action 5; Ans. 5.) According to the Examiner, the foregoing process would "necessarily, inherently, and implicitly create isolated CTLs that recognize a complex between SEQ ID NO: 166 and the HLA serotype present in the leukemia patient." (*Id.*)

The Examiner notes that while Gaiger does not "explicitly teach the use of the disclosed invention with HLA-A26 positive individuals," it would

have been obvious to do so in light of Yashiki's teaching that "individuals having HLA-A*26 are predisposed to leukemia." (Final Action 6.)

The Examiner finds that "there would be a reasonable expectation of success, because [Gaiger] teaches that the disclosed methods may be used to prevent, delay, or treat a disease associated with WT1 expression, and also explicitly disclose that leukemia is one such disease" and "because the instant claims are drawn to a CTL that is created using a known peptide in a known patient population (i.e., leukemia) via known and routine methods in the art, which predictably yield CTLs, and the known peptide is explicitly taught to for use in said patient population." (Final Action 6–7.)

We disagree with the Examiner's factual finding that the prior art provides a reasonable expectation of success of using SEQ ID NO: 166 in a patient population that had HLA-A26 to prevent, delay, or treat leukemia. Gaiger's treatment method requires incubating T cells isolated from the patient with a WT1 peptide to raise CTL against that peptide. (*See e.g.*, Gaiger ¶¶ 32–34, 76.) That leukemia is a disease associated with WT1 and that individuals having HLA-A26 are predisposed to leukemia do not by themselves give rise to an expectation of SEQ ID NO: 166 being able to prevent, delay or treat leukemia, because those facts imply nothing with respect to being able to raise CTLs against any particular WT1 peptide. That is, in order to have a reasonable expectation of success of using Gaiger's treatment method to treat an HLA-A26 positive leukemia patient using SEQ ID NO: 166, there must at least be a reasonable expectation that SEQ ID NO: 166 would yield CTLs. And, as noted by Appellant (Reply Br. 11), the Examiner admits that "the prior art does not provide guidance or

experimental support directing an artisan to specifically select SEQ ID NO: 166 with a reasonable expectation of successfully [] inducing CTL formation in HLA-A26 patients." (Ans. 8.)

Moreover, we disagree with the Examiner that combining the method of Gaiger (using SEQ ID NO: 166) with an HLA-A26 positive individual (that is predisposed to leukemia according to Yashiki) renders the claimed invention obvious. (Final Action 5; Ans. 5.) As Appellant points out, Gaiger clearly demonstrates that "predicted binding or even actual binding of an antigen peptide to an HLA type is not enough to expect CTL induction by the peptide." (Reply Br. 11.) Gaiger Example 4, tables 47 and 48 and accompanying discussion, demonstrate that, even where certain WT1 peptide sequences were predicted to bind with high scores, they did not in fact bind. (Gaiger ¶ 377 (Table 48 noting several peptides with binding percentages in the range of the "Negative control").) Thus, Gaiger notes that "some," not all, WT1 peptides predicted to bind HLA "can bind to class I MHC molecules, which is essential for generating CTL." (Gaiger ¶ 377.) In addition, Gaiger further notes that based on chromium release assays conducted, it was determined that of the peptides that were determined to bind HLA at levels greater than the "Negative control," not all "were able to elicit peptide specific CTL." (*Id.*)

Yashiki merely shows that individuals having HLA-A26 are predisposed to leukemia. In the absence of positive evidence that SEQ ID NO: 166 binds to HLA-A26, much less a prediction that it binds, there is no reason for one of ordinary skill in the art to use this peptide in the "basic methodology" Gaiger discloses for treating WT1 associated diseases, i.e.,

incubating T cells isolated from the patient with SEQ ID NO 166 to raise CTL against this peptide, much less in a leukemia patient having HLA-A26.

"[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a prima facie case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). In light of the foregoing, we agree with Appellant that "based on Gaiger and Yashiki[,] the skilled artisan would not reasonably consider using SEQ ID NO: 166 in HLA-A26 positive patients." (Reply Br. 13.) Thus, we conclude that the Examiner has not established a prima facie case of obviousness.

For the foregoing reasons, we reverse the rejection of claims 19 and 25 under 35 U.S.C. § 103 as unpatentable over Gaiger and Yashiki.

II

§101

The Examiner finds that claims 19 and 25 are directed to patent ineligible subject matter because evidence indicates that "WT1-specific CTLs are spontaneously formed in tumor-bearing HLA-A26 patients"[4] and the term "isolated" does not confer a "marked difference from the product's naturally occurring counterpart." (Ans. 16.) According to the Examiner, the evidence points to the claimed CTLs being naturally occurring because a) Sugiyama "clearly states that 'WTl-specific cytotoxic T lymphocytes and

[4] The Examiner cites Haruo Sugiyama, *WTJ (Wilm's Tumor Gene 1): Biology and Cancer Immunotherapy*, 40(5) Japanese Journal of Clinical Oncology, 377–387 (2010), in support of the foregoing.

WT1 antibodies are spontaneously induced in tumor-bearing patients' *(see, e.g.,* Sugiyama at 377; *see also id.* at 383–384)," and b) "the prior art teaches that HLA-A26 patients are pre-disposed to having leukemia and that leukemia-bearing HLA-A26 patients are well-documented (*see*, *e.g.*, Yashiki at 1047, 1059), and notably SEQ ID NO: 9 is a fragment of naturally occurring WT1 protein." (Ans. 15–16.)

It is our opinion that the Examiner failed to meet his burden of establishing a prima facie case that the claimed isolated CTL is directed to patent ineligible subject matter. As Appellant notes, "the Examiner has not offered anything, [from] Sugiyama or Yashiki, to support the allegation that [] a CTL that recognizes a complex between SEQ ID NO: 9 and HLA-A26 antigen is naturally occurring." (Reply Br. 16.) The fact that a "mechanism may exist [naturally in the body] in tumor bearing patients that may spontaneously induce WT1-specific [CTLs in tumor-bearing patients]" does not establish that HLA-A26 leukemia patients produce CTL's that specifically recognize a complex between a peptide of the amino acid of SEQ ID NO: 9 and HLA-A26. The Examiner does not provide evidence that because SEQ ID NO: 9 is a fragment of naturally occurring WT1 protein that this sequence is present in leukemia patients or HLA-A26 positive leukemia patients. Even if such evidence were presented, the existence of a mechanism that may spontaneously induce WT1-specific CTLs does not establish that, if HLA-A26 leukemia patients were to have the WT1 peptide fragment SEQ ID NO: 9, this sequence complexes with HLA-A26 *in vivo*, or that the complex elicits a CTL response. Sugiyama does not show that nor does Yashiki. And indeed, as discussed with respect

to the Examiner's obviousness rejection above, there is not even a reasonable expectation that complexation with HLA-A26 necessarily occurs based on predicted binding of this sequence with other HLA peptides. As Appellant notes, "[a]ll that the Examiner has demonstrated is that a mechanism may exist in tumor-bearing patients that may spontaneously induce WTl-specific cytotoxic T lymphocytes and WT1 antibodies." (Reply Br. 15.) That is a far cry from establishing the claimed CTLs exist in any HLA-A26 positive leukemia patient.

For the foregoing reasons, we reverse the rejection of claims 19 and 25 under 35 U.S.C. § 101 as being directed to patent ineligible subject matter.

SUMMARY

We reverse the rejection of claims 19 and 25 under 35 U.S.C. § 103 as unpatentable over Gaiger and Yashiki.

We reverse the rejection of claims 19 and 25 under 35 U.S.C. § 101 as being directed to patent ineligible subject matter.

REVERSED