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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MARIA ANTONIA VITIELLO

Appeal 2019-003997
Application 14/594,757
Technology Center 1600

Before FRANCISCO C. PRATS, TAWEN CHANG, and DAVID COTTA, *Administrative Patent Judges.*

CHANG, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 32, 34, 35, 42, and 44–60. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as PersImmune Inc. Appeal Br. 3.

BACKGROUND

"To become a cancer cell, a healthy cell undergoes multiple somatic mutations. Such mutations may be targets of the adaptive immune system, which performs the function of recognizing and eliminating small variations from self." Spec. ¶ 5 (citations omitted). According to the Specification, "[t]he idea of employing the adaptive immune system to kill cancer cells without harming normal cells has been a goal for many decades"; however, "tumor antigen identification and its translation to immunotherapy still face many problems" and "being able to define antigens in an easier and more efficient manner is an advantage." *Id.* ¶¶ 5–6. Further according to the Specification, "[t]his invention relates to the identification of mutations in expressed genes of cancer cells from cancer patients and use of the mutations to prepare cancer vaccines and adoptive immune cell therapies." *Id.* ¶ 3.

CLAIMED SUBJECT MATTER

The claims are directed to methods for producing cancer cell-specific cytotoxic T lymphocytes (CTLs). Claim 32 is illustrative:

> 32. A method for producing cancer cell-specific cytotoxic T lymphocytes (CTLs), comprising:
>
> a) providing exome sequences and transcriptome sequences from cancer cells of a subject;
>
> b) providing a set of exome mutations of the cancer cells generated by comparing the exome sequences from step a) to a reference human genome sequences;
>
> c) providing a set of cancer cell mutations generated by comparing the set of exome mutations of the cancer cells from step b) to the transcriptome sequences of the cancer cells of step a) and selecting identical mutations;
>
> d) providing exome sequences, and optionally transcriptome sequences, from normal cells of a HLA-matched donor;

e) selecting mutations unique to the cancer cells of said subject to provide a set of cancer cell-specific mutations, wherein selecting mutations unique to the cancer cells of said subject comprises comparing the cancer cell mutations from step c) to the exome sequences, and optionally to the transcriptome sequences, of step d);

f) making a plurality of isolated peptides having the cancer cell-specific mutations of step e); and

g) contacting mononuclear cells from the HLA-matched donor with one or more of the isolated peptides of step f) for a sufficient time to provide CTLs specific for the cancer cell-specific mutations, wherein the mononuclear cells from the HLA-matched donor comprise antigen presenting cells and T cells.

Appeal Br. 24 (Claims App.).

REJECTION(S)

A. Claims 32, 34, 35, 42, and 44–60 are rejected under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Hacohen,[2] Castle,[3] Johnston,[4] Leen,[5] and Lee.[6]

B. Claims 32, 34, 35, 42, and 44–60 are rejected under pre-AIA 35 U.S.C. § 112, 1st paragraph for failing to comply with the written description requirement.

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[2] Hacohen et al., US 2011/0293637 A1, published Dec. 1, 2011.
[3] John C. Castle et al., *Exploiting the Mutanome for Tumor Vaccination*, 72 CANCER RES. 1081 (2012).
[4] Johnston et al., US 2009/0186042 A1, published July 23, 2009.
[5] Leen et al., US 2011/0182870 A1, published July 28, 2011.
[6] Lee et al., *Monocyte-derived Dendritic Cells from HLA-Matched Allogeneic Donors Showed Greater Ability to Induce Leukemic Cell-Specific T Cells in Comparison to Leukemic Cell-Derived Dendritic Cells or Monocyte-Derived Dendritic Cells from AML Patients*, 32 LEUKEMIA RES. 1653 (2008).

OPINION

A. Obviousness rejection over Hacohen, Castle, Johnston, Leen, and Lee (claims 32, 34, 35, 42, and 44–60)

1. Issue

The Examiner finds that the combination of Hacohen, Castle, and Johnston teaches almost all of the limitations of the claims, except that none of these references "specifically disclose contacting mononuclear cells from the cancer patient or from the HLA-matched donor with the one or more cancer cell-specific antigens for a sufficient time to provide CTLs specific for the cancer cell-specific antigen." Final Act. 7. However, the Examiner finds that "Leen disclose[s] that antigen specific CTLs can be generated from patients or their HLA-matched allogeneic donors" and that "Lee disclose[s] that CTLs and dendritic cells [(i.e., APCs)] generated using mononuclear cells from HLA[-]matched donors resulted in an enhanced CTL response to autologous acute myeloma leukemia cells compared to autologous mononuclear cells." *Id.* (citation omitted). The Examiner concludes that, based on the teachings of Leen and Lee, it would have been obvious to a skilled artisan to modify the method made obvious by the combination of Hacohen, Castle, and Johnson to arrive at the claimed invention, because "Hacohen, Johnston[,] and Leen all disclose generating antigen specific CTLs to HLA-matched target cells" and "Lee disclose[s] the advantages of using HLA-matched allogeneic mononuclear cells for CTL activity." *Id.*

Appellant argues that the independent claims recite a method for production of cancer cell-specific CTLs comprising a step of contacting isolated peptides having cancer cell-specific mutations with mononuclear

cells from an HLA-matched donor comprising ***both*** antigen presenting cells ***and*** T cells and that the cited prior art combination does not teach or suggest this limitation. Appeal Br. 13–16. Appellant further argues that a skilled artisan would not have had a reason to combine the teachings of the cited references in the manner proposed by the Examiner. *Id.* at 16–17.

Appellant does not separately argue the claims. We therefore focus our analysis on claim 32 as representative. The issue with respect to this rejection is whether a preponderance of evidence of record supports the Examiner's conclusion that, based on the cited prior art combination, it would have been obvious to a skilled artisan to produce cancer cell-specific CTLs by "contacting mononuclear cells from [an] HLA-matched donor with one or more . . . peptides" isolated as recited in steps a) through f) of claim 32, wherein "the mononuclear cells from the HLA-matched donor comprise antigen presenting cells and T cells."

2. Findings of Fact

1. Hacohen teaches "a method of identifying . . . neoantigens that . . . serve as active pharmaceutical ingredients of vaccine compositions which stimulate anti-tumor responses," particularly "a tumor specific T-cell response" such as "a specific cytotoxic T-cell[] response and/or a specific helper T-cell response," wherein "'[n]eoantigen' means a class of tumor antigens which arises from tumor-specific mutations in expressed protein." Hacohen Abstract, ¶¶ 5, 70, 120.

2. In particular, Hacohen teaches

> a method of vaccinating or treating a subject for cancer by identifying a plurality of tumor specific mutations in an expressed gene of the subject, identifying mutant peptides or polypeptides having the identified tumor specific mutations,

> selecting one or more of the identified mutant peptide or polypeptides that binds to a class I HLA protein preferably with a greater affinity than a wild-type peptide and is capable of activating anti-tumor CD8 T-cells, and administering to the subject the one or more selected peptides, polypeptides or autologous dendritic cells or antigen presenting cells pulsed with the one or more identified peptides or polypeptides.

Id. ¶ 12.

3. Hacohen teaches an "approach to identify tumor-specific neoepitopes involv[ing] three steps":

> (1) identification of DNA mutations using whole genome or whole exome (i.e. only captured exons) or RNA sequencing of tumor versus matched germline samples from each patient; (2) application of validated peptide-MHC binding prediction algorithms to generate a set of candidate T cell epitopes that may bind patient HLA alleles and are based on non-silent mutations present in tumors; and (3) optional demonstration of antigen-specific T cells against mutated peptides or demonstration that a candidate peptide is bound to HLA proteins on the tumor surface.

Id. ¶ 50; *see also id.* ¶¶ 36, 54, 60 (describing the method as using "massively parallel genomic sequencing of the entire coding portion of a cancer patient genome to identify the specific mutated genes in a tumor"), 176–177 (Example 1), 179–180 (Example 2, sequencing whole genomic DNA or coding exons and generating and sequencing DNA and RNA libraries).

4. Hacohen teaches inducing "ex vivo CTL responses to a particular tumor antigen . . . by incubating in tissue culture the patient's CTL precursor cells (CTLp) together with a source of antigen presenting cells (APC) and the appropriate peptide." *Id.* ¶ 163. Hacohen teaches that "[a]fter an appropriate incubation time . . . , in which the CTLp are activated and mature and expand into

effector CTL, the cells are infused back into the patient, where they will destroy their specific target cell (i.e., a tumor cell)." *Id.*

5. Hacohen teaches that, based on its study to date, "[f]or chronic lymphocytic leukemia, . . . there are an average of 23 protein-altering mutations per patient, 46 predicted binding mutant peptides and 15–25 validated binding mutant peptides."

6. Castle discloses a study with the objective of "identify[ing] potentially immunogenic somatic point mutations in B16F10 mouse melanoma by NGS [(next generation sequencing)] and . . . test[ing] these for *in vivo* immunogenicity by peptide vaccination of mice measuring elicited T-cell responses." Castle 1083, left column.

7. Castle teaches extracting in triplicate DNA and RNA from B16F10 melanoma (cancer) cells, as well as DNA from tail tissue of C57BL/6 mice as wild-type background genome; carrying out exome capture for DNA resequencing; preparing mRNA-seq cDNA libraries from total RNA; aligning RNA reads to reference genome and transcriptome; determining gene expression; and aligning DNA reads to the reference genome. *Id.* at 1082, left column, 1083, bridging paragraph.

8. Castle teaches that, for its study, "[m]utations were selected that were: (i) present in all B16F10 and absent in all C57BL/6 triplicates, (ii) FDR [(false discovery rate)] ≤ 0.05, (iii) homogeneous in C57BL/6, (iv) occur in a RefSeq transcript, and (v) cause nonsynonymous changes." *Id.* at 1082, left column, 1083, right column–1084, left column. Castle teaches that "[f]urther mutation

selection criteria were occurrence in B16F10-expressed genes . . . and in an MHC-binding peptide." *Id.* at 1082, bridging paragraph, 1084, left column.

9. Castle teaches that "[w]hole-exome sequencing in combination with transcriptome profiling enables the discovery of the expressed protein coding mutanome and provides insight into the molecular nature of potential driver mutations in B16F10 melanoma." *Id.* at 1088, right column.

10. Castle's study "used next generation sequencing exome resequencing to identify 962 nonsynonymous somatic point mutations in B16F10 murine melanoma cells, with 563 of those mutations in expressed genes." *Id.* at Abstract; *see also id.* at 1084, left column.

11. Castle teaches that its study "show[s] . . . a correlation between tumor mutations and the epitope landscape by *in vivo* data, demonstrating that many nonsynonymous somatic mutations in tumors are immunogenic and confer antitumoral vaccine activity." *Id.* at 1082, left column. In particular, Castle teaches that "one-third (16 of 50) of the [selected] mutated epitopes to be immunogenic" and that "[n]early half of these epitopes induced a strong T-cell response that matches the intensity observed for . . . one of the most immunogenic B16 melanoma target antigens." *Id.* at 1089, right column.

12. Castle teaches that its study

> has implications for human cancer therapies. . . . [T]he approach opens a new dimension for individualized immunotherapy and adds to tailored vaccine concepts that were previously suggested . . . . Every patient's tumor bears a highly individual mutation "signature," and more than 95% of mutations are unique and patient specific. Thus, a vaccine concept based on the

> multiplicity of mutated epitopes would require profiling of each patient's tumor to determine the unique mutation signature. Dramatically reduced costs and time required for genome-wide discovery of cancer-specific mutations opens the door for individualized immunotherapy of cancer patients. In particular, in advanced disease with tumor genomes becoming more unstable, individualized T-cell therapies may outdo other treatment options as accumulation of mutations allows to combine even more antigens, thereby counteracting the selection of antigen loss variants during immunotherapy and tumor evolution.

Id. at 1090, bridging paragraph (citations omitted).

13. Johnston teaches that methods for identifying tumor specific vaccine antigens comprise "identifying novopeptides and/or novopeptide nucleic acid sequences that are likely to be expressed and/or are experimentally determined to be expressed in one or more cancerous cell types" and "immunological screening of the novopeptides so identified . . . for suitability as a component of a vaccine." Johnston ¶ 40.

14. Johnston teaches "novopeptides identified by the presence of frameshift mutations in tumor genes previously not identified as being oncogenic," wherein novopeptides are tumor-specific antigens (TSAs), and the use of such peptides for the treatment of cancer. *Id.* at Abstract, ¶ 25; *see also id.* ¶ 29 (screening for TSAs by assaying for frameshifts in RNA extracted from tumor cell), 31 (novopeptides may be identified by comparing cancer genome with expression database or by sequencing nucleic acids to detect alternations in DNA and RNA), 43 (RNA sequences are an important source of data for identification of candidate novopeptides because many novopeptide associated mutations results from events occurring at the level of RNA processing and/or translation).

15. Johnston teaches "methods for immunologically screening for a

T cell response to a . . . novopeptide comprising first preparing . . . CTL's . . . having T cell receptors specific for the novopeptide as displayed in MHC or HLA," and then testing the CTL's "for reactivity against each of (1) cancerous cells, and (2) non-cancerous cells, each having an MHC or HLA type matching that of the MHC or HLA for which the CTL's are specific." *Id.* ¶ 51; *see also id.* ¶¶ 247–248 (describing an example CTL assay showing that "CTLs activated against novopeptide 6-21 . . . were able to kill MHC-matched tumor cells pulsed with 6-21 peptide[] but not unpulsed SW480 tumor cells").

16. Johnston teaches "any immunoassay that can measure a T cell response can be used in the disclosed methods" and that such methods include identifying novopeptides by "using immune assays of human cancer patient peripheral blood mononuclear cells (PBMCs) or animal tumor model (PBMCs) to detect reactivity to the novopeptide." *Id.* ¶ 32.

17. Leen teaches "methods . . . for the generation and use of cytotoxic T lymphocytes that target multiple viruses or that are specific for multiple tumor antigens." Leen Abstract; *see also, e.g., id.* ¶¶ 21, 51.

18. Leen teaches using CTLs, including CTLs of its invention, for treating individuals with cancer having particular tumor-associated antigens. *Id.* ¶¶ 10, 12, 14, 52.

19. Leen teaches that dendritic cells (DCs) are "the most powerful antigen-presenting cells known," that "[s]timulation of peripheral blood (PB) T cells with mature dendritic cells (DC) expressing antigen, can lead to reactivation of antigen-specific cytotoxic T lymphocytes (CTL)," and that "DC can be differentiated from adherent PB mononuclear cells (PBMC) by culture in GM-CSF and IL-4." *Id.* ¶ 104.

20. Leen teaches generation of multivirus CTL lines wherein "dendritic cells [are] pulsed with pepmixes spanning the viral antigens . . . to produce antigen-presenting cells (APCs)." *Id.* ¶ 15. Leen teaches that, "[a]lternatively, PBMCs [(peripheral blood mononuclear cells)] can be stimulated directly with pepmixes to activate antigen-specific cells." *Id.* Similarly, Leen teaches that to generate multi-tumor associated antigen (TAA) CTL, "DCs may be pulsed with pepmixes spanning the target antigen." *Id.*

21. Leen teaches generating tumor antigen specific CTL lines in healthy donors. *Id.* ¶¶ 30–31, Figs. 1, 2; *see also id.* ¶ 227 (donor-derived Epstein-Barr Virus (EBV)—CTL lines can safely protect patients against the development of EBV-driven lymphomas and cure patients even with bulky established disease), ¶¶ 234, 237 (example of generating TAA-specific CTL from healthy donors), ¶ 252 (injection of autologous *or allogeneic* TAA-specific CTLs in individuals with Hodgkin's or non-Hodgkin's lymphoma); *cf.* ¶ 121(donor-derived multivirus-specific CTL lines).

22. Leen teaches preparing DCs from a patient *or a donor* for use as APCs. *Id.* ¶¶ 114–115.

23. Leen teaches methods for generating CTLs using APCs and T cells from the PBMCs of the same individual. *See, e.g., id.* ¶¶ 27–29 (describing method of generating CTLs targeting viral or tumor antigens comprising the steps of (1) contacting dendritic cells from an individual with peptides spanning part or all of an antigen to produce APCs presenting epitopes from such antigens and (2) contacting PBMCs *from individual with the APCs*), ¶¶ 105–107 (teaching a procedure for preparing dendritic cells as a component required for the generation of therapeutic T cells, comprising

among other things adhering DC precursors from PBMCs and *cryopreserve non-adherent cells for future use as responder T cells*), ¶ 177 (initiating a trivirus-specific CTL line by generating monocyte-derived DCs using plastic adherence, culturing and maturing the DCs, nucleofecting the DCs with plasmids expressing viral antigens, and *stimulating virus specific T cell retained from the non-adherent PBMC fraction*).

24. Leen teaches a method for generating cytotoxic T-cells wherein both APCs and T cells used in the method are derived from the mononuclear cells of a donor. In particular, Leen teaches "a method for generating donor-derived multivirus-specific cytotoxic T-cells to treat and/or prevent viral infection and/or reactivation in a subject in need of such treatment," comprising among other steps:

> (i) isolation of peripheral blood mononuclear cells (PBMCs) from a donor; (ii) generation of antigen-presenting cells (APCs) called dendritic cells from the PBMCs by selecting for the ability to adhere to a cell culture substrate . . . ; (ii[i]) separate nucleofection of DCs with plasmid DNA expression vectors that encode at least one viral protein from at least two viruses . . . [(iv)] co-culturing the nucleofected DCs with T-cells retained from the non-adherent PBMC fraction; . . . and ([vii]) verifying the antigen specificity and lack of alloreactivity of the stimulated T-cells."

Id. ¶ 20; *see also id.* ¶ 270 (describing method for generation of tumor-specific CTL lines as requiring the generation of several different components from peripheral blood mononuclear cells (PBMC), wherein "[b]lood may be collected from the patient or the allogeneic stem cell donor" and "T cells and monocyte-derived dendritic cells (DCs) . . . prepared from fresh or cryopreserved PBMC).

25. Leen teaches using CTLs from HLA-matched donors. *Id.* ¶¶

180, 275 (stating in the design of certain embodiments of the invention that release criteria for administering CTL to patients include *HLA identity*); *see also id.* ¶¶ 10, 253 (teaching preparing CTLs whose specificity was directed towards Epstein-Barr viral antigens expressed by tumor cells "by sequentially using dendritic cells (DCs) and then [EBV-transformed lymphoblastoid cell lines (EBV-LCL)] genetically modified to overexpress LMP1 and LMP2 (two of the three antigens) to reactivate and expand LMP-specific CTLs from patients *or their HLA-matched allogeneic donors*").

26. Leen "underscores the importance of identifying appropriate antigens that are not expressed or poorly expressed on normal tissues and of optimizing cell culture conditions for tumor-specific CTL production, to overcome the mechanisms that establish T cell tolerance against 'self' antigens." *Id.* ¶ 11; *see also id.* ¶ 254.

27. Leen teaches embodiments of its invention in which "the CTL . . . is designed to specifically correspond to the antigenic expression pattern exhibited by the individual's tumor" such that "a . . . CTL product is generated that responds to the unique antigenic signature of an individual's tumor." *Id.* ¶ 25; *see also id.* ¶ 255 (describing unique tumor associated antigens resulting from single mutations that are tumor and patient specific and considered ideal for immunotherapy).

28. Lee's study "compare[s] the generation of leukemia-cell-specific cytotoxic T lymphocytes (CTLs) that were stimulated *in vitro* by allogeneic monocyte-derived DCs (allogeneic mDCs) from HLA-matched sibling donors, leukemic DCs from AML patients or autologous mDCs from the AML patients." *Id.* at 1654–1655, bridging paragraph.

29. Lee teaches that the purpose of its study "was to evaluate the

feasibility of using HLA-matched allogeneic monocyte-derived DCs pulsed with leukemic cell lysates *in vitro* for patients with AML." *Id.* at 1658, left column.

30. Lee discusses prior studies wherein "[c]omparison of the use of allogeneic or autologous treatment revealed that there was no adverse effect and no differences in clinical outcome." *Id.* at 1659, left column.

31. Lee teaches that "[a]llogeneic[]mDCs generated from HLA-matched donors have several advantages compared to autologous mDCs or leukemic DCs from AML patients, including easy accessibility of monocytes from healthy normal control donors." *Id.* at 1658, right column.

32. Lee teaches that "HLA-matched healthy sibling donors [were used] to avoid MHC incompatability for antigen presentation of DCs to T cells." *Id.* at 1659, left column.

33. The allogeneic mDCs used in Lee were induced from CD14+ cells isolated from the peripheral blood of HLA-matched sibling donors. *Id.* at 1655, bridging paragraph, 1656, right column.

34. Lee teaches that "[a]llogeneic mDCs showed higher expressions of several molecules (HLA-DR, CD80, CD83, or CD86), higher production of IL-12 and higher capacity to stimulate allogeneic T cells compared to both leukemic DCs and autologous mDCs." *Id.* at Abstract, 1656, right column–1657, 1658, bridging paragraph, 1658–1659, bridging paragraph.

35. Lee teaches that "[a]utologous T cells primed by allogeneic mDCs displayed a larger number of interferon-γ-secreting cells against leukemic cells than those primed by either leukemic DCs or autologous mDCs." *Id.* at Abstract, 1657, 1658 bridging paragraph, 1658–1659,

bridging paragraph.

36. Lee teaches that its results "suggest that monocyte-derived DCs from HLA-matched allogeneic donors can be used as an alternative to generate leukemia-specific cytotoxic T cells and to overcome the limitations of leukemic DCs or autologous mDCs." *Id.* at Abstract, 1658 bridging paragraph, 1659, left paragraph.

3. *Analysis*

Unless otherwise noted, we adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Final Act. 4–9, Ans. 3–17; FF1–FF36) and agree that claim 32 is obvious over the cited prior art combination. We address Appellant's arguments below.

Appellant contends that "the use of ***both*** APCs and . . . T cells from the mononuclear cells from the HLA-matched donor in [the claimed] process . . . provides a notable point of innovation that was not taught or suggested by the prior art." Appeal Br. 12. Appellant first contends that Lee and Leen, cited by the Examiner for meeting the above limitation, do not disclose the limitation. *Id.* at 13. In particular, Appellant contends that Lee "discloses production of leukemia cell-specific CTLs by mixing APCs and T cells having ***different*** genetic backgrounds from each other" and that "the T cells of Lee . . . are explicitly disclosed as from 'healthy volunteers' and are never described as from the same donor as the mDC source of Lee." *Id.* at 14; *see also* Reply Br. 8. Appellant likewise contends that, while Leen describes the use of HLA-matched donor T cells, Leen "expressly require[s] the use of *autologous* (from the patient) APCs for virus-specific CTL production." Appeal Br. 15; *see also* Reply Br. 6–7.

We are not persuaded. As an initial matter, we disagree with Appellant's contention that Leen *requires* the use of autologous APCs, because Leen also teaches preparing DCs from a patient *or a donor* for use as APCs. FF22. Indeed, Leen teaches methods of generating CTLs using APCs and T cells from the PBMCs of the same individual, including from the PBMCs of a donor. FF23, FF24. Moreover, "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

In this case, Leen teaches at least the use of HLA-matched donor T cells to create tumor-associated antigen-specific CTLs (Appeal Br. 15, FF25), and Lee suggests not only that HLA-matched donor APCs may be used to generate leukemia-cell-specific CTLs, but also that such APCs showed higher expression/production of certain molecules involved in the immune response and higher capacity to stimulate allogeneic T cells than leukemic and autologous mDCs. Thus, we agree with the Examiner that the combination of Leen and Lee would have suggested to a skilled artisan a method of producing cancer cell-specific CTLs using "mononuclear cells from [an] HLA-matched donor . . . wherein the mononuclear cells from the HLA-matched donor comprise antigen presenting cells and T cells" as recited in claim 32.

Appellant argues that, "[t]o the extent that the rejection is based on the reasoning that one skilled in the art would have used the HLA-matched antigen presenting cells of Lee with the HLA-matched donor T cells of

Leen, . . . the Examiner has failed to articulate the requisite motivation for one of skill in the art to make that combination, nor has the Examiner provided a reasonable expectation of success in doing so." Appeal Br. 16. Appellant contends that, in any event, the Examiner's stated reasoning for combining the references and regarding reasonable expectation of success does not explain "why a skilled artisan *would* have substituted the APCs of Leen with the APCs from Lee for mixing with the T cells of Lee to arrive at T cells and APCs which are not just HLA-matched, but from the ***same*** HLA-matched donor." Reply Br. 8. Appellant contends that such omission is "notable in the face of Leen's strong and express preference for ***only*** the use of ***autologous*** APCs of the cancer patient" and that Hacohen "also expressly discloses a strong preference for use of autologous APCs" and T cells. Appeal Br. 16–17.

We are not persuaded. As discussed above, Lee suggests that allogeneic monocyte-derived DCs (allogeneic mDCs) from HLA-matched donors have advantages as compared to autologous or leukemic DCs, including easy accessibility of monocytes from healthy normal control donors (FF31) and also results in superior immunostimulatory effect when used with either allogeneic or autologous T cells (FF34–FF36). Thus, we agree with the Examiner that a skilled artisan would have reason—i.e., to overcome the limitations of leukemic or autologous mDCs as taught by Lee–and a reasonable expectation of success, of using mDCs and T cells from HLA-matched donors to produce cancer cell-specific CTLs.

As for Appellant's argument that Lee and Leen do not provide a reason for, or reasonable expectation of success of, using mDCs and T cells from the *same* HLA-matched donor, we are also unpersuaded. The Supreme

Court explained in *KSR* that obviousness analysis "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ" and that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416, 418 (2007). Given that Lee and Leen suggest using APCs and T cells from HLA-matched donors to produce cancer-specific CTLs, we agree with the Examiner that it would have been obvious to use the APCs and T cells from the same HLA-matched donor, absent evidence that such a combination yielded unpredictable results. This is particularly the case given that Lee expressly teaches that APCs and T cells used for generating CTLs may be obtained from the PBMCs of the same individual, including PBMCs of donors. FF23, FF24.

Finally, we are not persuaded by Appellant's argument that the claims are not obvious because of "Leen's strong and express preference for ***only*** the use of ***autologous*** APCs of the cancer patient" and Hacohen's express disclosure of "a strong preference for use of autologous APCs" and T cells. Appeal Br. 16–17. As discussed above, we disagree with Appellant that Leen teaches that only autologous APCs should be used in its method. FF22, FF24. The portions of Hacohen cited by Appellant do not support Appellant's contention that Hacohen expressed a strong preference for using autologous APCs and T cells. More specifically, while Hacohen describes using autologous APCs and T cells for its methods, failure to mention an alternative (i.e., HLA-matched donor APCs and T cells) is not the same as a stated *preference* for using autologous APCs and T cells over HLA-matched donor APCs and T cells.

Appellant's citation to *Polaris Industries v. Arctic Cat*, 882 F.3d 1056 (Fed. Cir. 2018) is inapposite. In *Polaris*, appellant Polaris introduced undisputed evidence that a proposed modification in a prior art all-terrain vehicle (ATV) "would have required significantly raising the occupancy area," which a prior art reference taught would have resulted in raising the ATV's center of gravity and "'a decrease in vehicle stability and subsequent increased risk of rollovers.'" *Id.* at 1067. The Federal Circuit held that the Board: did not conduct a proper teaching away analysis, using instead a "subjective preference" analysis that "disregard[ed] certain teachings as ill-defined 'subjective preferences'" and thus "invited . . . 'hindsight bias'"; "focused on what a skilled artisan would have been *able* to do, rather than what a skilled artisan would have been *motivated* to do at the time of the invention"; and "encourage[d] the fact-finder to . . . discard evidence relevant both to 'teaching away' and . . . motivat[ion] to combine references." *Id.* at 1068–1069. The Federal Circuit further explained that, "even if a reference is not found to teach away, its statements regarding preferences are relevant to a finding regarding whether a skilled artisan would be motivated to combine that reference with another reference." *Id.* at 1069.

In contrast, in the instant case the combination of references provides an express reason to use Lee's HLA-matched donor APCs in a method for producing cancer cell-specific CTLs, including with donor T cells such as those described by Leen – namely that such donor APCs have certain advantages in comparison to autologous or leukemic APCs in producing cancer-cell specific CTLs. FF31, FF34–36. Neither does Appellant point to any suggestion in the prior art that use of HLA-matched donor APCs is

disadvantageous, or any expressed preference in the art for using autologous APCs *over HLA-matched donor APCs*. Instead, as discussed above, Appellant points at most to the fact that a prior art reference (Hacohen) does not discuss using HLA-matched donor APCs in its method.[7]

Accordingly, we affirm the Examiner's rejection of claim 32 as obvious over the combination of Hacohen, Castle, Johnston, Leen, and Lee. Claims 34, 35, 42, and 44–60, which are not separately argued, fall with claim 32.

B. Written description rejection (claims 32, 34, 35, 42, and 44–60)

1. Issue

The Examiner finds that "the cancer cell-specific antigens [of the claims] are identified by function, [i.e.,]the capability of producing cancer cell-specific cytotoxic T lymphocytes which, by definition, would be capable of killing the subject's cancer cells." Final Act. 3. The Examiner finds that the Specification does not adequately describe the claims because the Specification "does not describe any cancer cell-specific antigens that has [the] described functions" of "producing cancer cell-specific cytotoxic T lymphocytes [that] are capable of killing a subject's cancer cells," only "how to obtain possession of these cancer cell-specific antigens." *Id.*

Appellant argues that the claims are not directed to cancer cell-specific mutations but rather to "methods for improved T cell generation, with a point of innovation being the use of both antigen presenting cells and the T cells from the mononuclear cells from the HLA-matched donor, and

[7] As discussed above, Leen teaches using either donor-derived or autologous APCs. FF22, FF24.

then contacting these cell populations with peptides encoding for a subject's cancer cell-specific mutations to generate CTLs." Appeal Br. 19. Appellant further argues that the Examiner's position on the written description rejection is contrary to the "positions simultaneously taken by the Examiner for establishing what is known to a person of ordinary skill in the art" in the obviousness rejection. *Id.* at 19–20.

The issue with respect to this rejection is whether a preponderance of the evidence of record supports the Examiner's finding that the Specification does not adequately describe the claims.

2. Analysis

"[T]he test for sufficiency [of written description] is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). On balance we agree with Appellant that the Examiner has not established a prima facie case that the claims fail to comply with the written description requirement.

The Examiner finds that "[t]he claimed invention . . . includes a step for using . . . yet to be identified . . . cancer specific peptides for making CTLs" and that "the bottleneck in this invention is selecting correct peptides." Ans. 20. The Examiner finds that the Specification "only disclose[s] methods for identifying cancer cell mutations and selecting peptides with cancer specific mutations with potential HLA binding motifs," but "does not disclose any cancer cell-specific peptides capable of producing cancer cell-specific CTLs." *Id.* at 21. Citing *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 927 (Fed. Cir. 2004), the Examiner asserts

that '[p]ossession [of a claimed genus] may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features." Ans. 22. The Examiner also distinguishes the present claims from those in *In re Herschler*, 591 F.2d 693 (CCPA 1979), "because the structure of the steroids claimed [in] *In re Herschler* were known in the art," while in the instant case "[t]he structure of the cancer-cell specific peptides is not known," and

> [t]he Specification does not demonstrate any examples in which cancer-specific peptides were used to produce a cancer cell-specific cytotoxic T lymphocytes nor disclose any reference in which any cancer-specific peptides encompassed by the present claims were identified as being capable of producing a cancer cell-specific cytotoxic T lymphocytes.

Ans. 22–23.

We are not persuaded. While we acknowledge certain similarities exist between the present claims and those found to lack written description in *Rochester*, we find that this case to be distinguishable.

The claims in *Rochester* related to "methods 'for selectively inhibiting PGHS-2 activity in a human host' by 'administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to [or in] a human host in need of such treatment,'" wherein PGHS-2 is the enzyme prostaglandin H synthase-2. *Rochester*, 358 F.3d at 918. While the patent at issue in *Rochester* (the '850 patent) contained descriptions of "'assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product[,] and methods of treating diseases characterized by aberrant PGHS-2 activity using such compounds," it was undisputed in *Rochester* that the specification "[did] not disclose any

compounds that can be used in its claimed methods." *Id.* at 927. Indeed, the Federal Circuit found that no evidence was presented that such a compound was even known. *Id.* The Federal Circuit explained that, in short, "the [specification] does not disclose just 'which 'peptides, polynucleotides, and small organic molecules' have the desired characteristic of selectively inhibiting PGHS-2," and, thus, "[t]he claimed methods . . . cannot be practiced based on the patent's specification, even considering the knowledge of one skilled in the art." *Id.*

In contrast to the disclosures in *Rochester* that merely describe an assay for determining whether a compound inhibits PGHS-2 activity, without describing, for instance, which non-steroid compounds should be tested or how such compounds may be arrived at, in the present case the steps set forth in claim 32 *result in* the "peptides having . . . cancer-specific mutations" that may be used in the claimed method for producing cancer cell-specific cytotoxic T lymphocytes. Unlike the claims in *Rochester*, therefore, the specification in the present case discloses compounds that are intended for use in the claimed method. For this reason, we are not persuaded by the Examiner's assertion that the claims are not adequately described because they "include[] a step for using . . . yet to be identified . . . cancer specific peptides for making CTLs."[8]

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[8] To the extent the Examiner's argument is that adequate written description requires disclosure of specific nucleotide or amino acid sequences of all cancer-specific mutations encompassed by the claims, we disagree. The claims are not to specific mutations, but to a method of identifying mutations and producing cancer-specific CTLs using peptides containing such mutations. "[T]he certainty required of [a patent] disclosure is not greater than that which is reasonable, having due regard to the subject matter

An alternative basis for the Examiner's rejection is that the Specification does not disclose *which* of the peptides having the cancer-specific mutations, if any, could be successfully used to contact mononuclear cells from HLA-matched donors to produce cancer cell-specific CTLs. While we understand the Examiner's position, we are not persuaded that the Examiner has established a prima facie case that the claims lack written description on this basis either.

In particular, the Specification discloses that "[f]urther selection of mutant sequences from the cancer cells that may be potential T cell epitopes for recognition by T lymphocytes (e.g., cytotoxic T lymphocytes) is achieved by evaluating peptides containing the mutation sequences for their ability to bind to MHC antigens that are expressed by the cancer patient" and that, in addition to synthesizing the peptides and testing them, "peptides containing mutant sequences of interest [may also be] evaluated for their ability to bind to HLA histocompatibility antigens of the cancer patient" using computer-based algorithm(s) for predicting HLA binding peptides. Spec. ¶¶ 10, 61, 63. The Specification explains that online T cell epitope prediction programs can be extremely accurate, with peptide sequences predicted to an accuracy of 95%. *Id.* ¶ 64. The Specification also provides example(s) in which cancer mutations are identified from exomic and transcriptomic libraries using next generation sequencing and in which

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involved." *Capon v. Eshhar*, 418 F.3d 1349, 1360 (Fed. Cir. 2005) (internal quotation marks omitted). Because cancer-specific mutations may be unique to a particular patient, *see, e.g.,* FF12, it would not be reasonable to require disclosure of all possible cancer-specific mutations encompassed by the claims. We note that the Specification does provide examples of certain leukemic specific sequences. *See, e.g.,* Spec. Figs. 4 & 5.

mutations with potential HLA binding motifs are further selected through a T cell epitope prediction program. *Id.* ¶¶ 100–119.

The Examiner acknowledges that the Specification discloses selecting cancer specific peptides having potential HLA binding motifs. However, the Examiner does not sufficiently explain why these disclosures would not "reasonably convey to those skilled in the art that the inventor had possession of the claimed" method for producing cancer cell-specific CTLs as of the time of the filing. Instead, the Examiner asserts only that the Specification "does not disclose any cancer cell-specific peptides capable of producing cancer cell-specific CTLs" or "any reference in which any cancer-specific peptides encompassed by the present claims were identified as being capable of producing a cancer cell-specific cytotoxic T lymphocytes." Ans. 21, 22–23.

As an initial matter, we note that actual reduction to practice is not required to satisfy the written description requirement. *Rochester*, 358 F.3d at 926. Therefore, the fact that the Specification does not include a working example in which a cancer cell-specific peptide is used to produce cancer-cell specific CTLs is not dispositive. Furthermore, in this case the Examiner has not explained why a skilled artisan would not reasonably believe that the cancer cell-specific peptides identified through the claimed steps would not be capable of producing cancer cell-specific CTLs, particularly when similar methods of producing CTLs and/or immune responses from cancer cell-specific peptides has been described in the prior art. *See, e.g.,* FF5 (Hacohen teaching that based on study to date there are an average of 15–25 validated binding mutant peptides per patient for chronic lymphocyte leukemia), FF11 (Castle teaching that one-third of its selected mutated epitopes were

immunogenic and nearly half of those induced a strong T-cell response). In this regard, we note that "the written description requirement may be satisfied 'if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure,'" and that "[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." *Capon*, 418 F.3d at 1357–1359.

It may be that a skilled artisan would dispute, for example, whether HLA binding motifs are sufficiently known in the art or whether knowledge of HLA binding motifs "gives the required kind of structure-identifying information" about cancer-specific mutations useful in the claimed method of producing cancer-specific CTLs. *See, e.g., Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1378 (Fed. Cir. 2017) (holding that claims to monoclonal antibody not adequately described by disclosure of antigen structure where "it has been . . . hotly disputed whether knowledge of the chemical structure of an antigen gives the required kind of structure-identifying information about the corresponding antibodies"). However, such evidence is not before us in this case.

Accordingly, we reverse the Examiner's rejection of claims 32, 34, 35, 42, and 44–60 as lacking adequate written description.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
32, 34, 35,	103(a)	Hacohen, Castle,	32, 34, 35,	

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
42, 44–60		Johnston, Leen, Lee	42, 44–60	
32, 34, 35, 42, 44–60	112 (pre-AIA), first paragraph	Lack of written description		32, 34, 35, 42, 44–60
Overall Outcome			32, 34, 35, 42, 44–60	

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