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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MALLEN HUANG

Appeal 2019-000281
Application 10/551,804
Technology Center 1600

Before FRANCISCO C. PRATS, JEFFREY N. FREDMAN, and TAWEN CHANG, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134 involving claims to a therapeutic composition. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

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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 the inventor, Dr. Mallen Huang (*see* Appeal Br. 1).

[2] We have considered and refer to the Specification of Sept. 30, 2005 ("Spec."); Final Action of Non-Final Office Action of Sept. 26, 2017 ("Non-Final Act."); Appeal Brief of Apr. 23, 2018 ("Appeal Br."); Examiner's Answer of Aug. 7, 2018 ("Ans."); and Reply Brief of Oct. 9, 2018 ("Reply Br.").

Statement of the Case

Background

"Vaccination approaches utilizing nucleotide sequences, including DNA or RNA sequences, have been developed during the last decade. DNA vaccines are easy to construct, stable and cost effective to produce" (Spec. 1:9–11). "[O]nce injected into a subject, the nucleotide sequence or nucleotide-sequence-comprising vector will be taken up by the subject's cells and expressed" (Spec. 16: 21–23). Then, "professional APCs [antigen presenting cells] either directly acquire antigen or take up antigens released from other transfected cells" (Spec. 16:25–27). "These APCs display peptide fragments of protein antigens, in association with MHC molecules, on its surface, and activates antigen-specific T cells" (Spec. 10:15–17).

The Claims

Claims 75, 76, 79–89, and 91–97 are on appeal. Claim 75 is representative and reads as follows:

> 75. A therapeutic composition, comprising a combined mixture of:
>
> a nucleic acid having a nucleotide sequence encoding a tumor associated antigen, wherein said nucleic acid is provided in a vector and under transcriptional control of a promoter, said vector comprises an unmethylated cytidine phosphate guanosine (CpG) sequence, and said vector is selected from at least one of virus vector, non-viral vector, plasmid, microbe-derived vector, liposome and small molecule carrier; and
>
> professional antigen-presenting cells in the form of plasmacytoid dendritic cells expressing Toll-like receptor 9 and modified for stable expression of at least one of CD40 ligand and GM-CSF encoded by a nucleotide sequence engineered into said antigen-presenting cells.

The issues

The Examiner rejected claims 75, 76, 79–89, and 91–97 under 35 U.S.C. § 103(a) as obvious over Crystal,[3] Hwu,[4] Krieg '067,[5] Schetter,[6] Schultze,[7] Krug,[8] Hornung,[9] Krieg '680,[10] Fonteneau,[11] Pullarkat,[12] and Brenner[13] (Ans. 3–6).

The Examiner rejected claims 75, 76, 79–89, and 91–97 under 35 U.S.C. § 103(a) as obvious over Crystal, Hwu, Krieg '067, Schetter, Schultze, Krug, Hornung, Krieg '680, Fonteneau, Pullarkat, Brenner, Ni,[14]

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[3] Crystal et al., US 2003/0202963 A1, published Oct. 30, 2003.
[4] Hwu et al., US 2004/0146492 A1, published July 29, 2004.
[5] Krieg et al., US 2004/0186067 A1, published Sept. 23, 2004.
[6] Schetter et al., US 2003/0181406 A1, published Sept. 25, 2003.
[7] Schultze et al., US 7,385,023 B1, issued June 10, 2008.
[8] Krug et al., *Toll-like receptor expression reveals CpG DNA as a unique microbial stimulus for plasmacytoid dendritic cells which synergizes with CD40 ligand to induce high amounts of IL-12*, 31 Eur. J. Immunology 3026–37 (2001).
[9] Hornung et al., *Quantitative Expression of Toll-Like Receptor 1-10 mRNA in Cellular Subsets of Human Peripheral Blood Mononuclear Cells and Sensitivity to CpG Oligodeoxynucleotides*, 168 J. Immunology 4531–7 (2002).
[10] Krieg, US 2004/0198680 A1, published Oct. 7, 2004.
[11] Fonteneau et al., *Activation of influenza virus specific CD4+ and CDS+ T cells: a new role for plasmacytoid dendritic cells in adaptive immunity*, Blood 1–48 (2003).
[12] Pullarkat et al., *Lymphoid Dendritic Cells Mobilized with Pregeniporitin Inducer Th1 and Peptide-Specific Cytotoxic T Cell Response*, Blood 297a, Abstract 1254 (2001), text unreadable.
[13] Brenner et al, *Transfusion Medicine: New Clinical Applications of Cellular Immunotherapy*, Hematology 356–75 (2000).
[14] Ni et al., *Detection of bcr/abl fusion transcripts by semiquantitative multiplex RT-PCR combined with a colormetric assay in Ph positive leukemia*, 124 Cancer Letters 173–80 (1998).

and Tanaka[15] (Ans. 6–7).

Because both of these rejections rely upon the same combination of references and Ni and Tanaka are solely added to address SEQ ID NOs: 3–5 (*see* Ans. 6), we will consider these rejections together.

The Examiner finds Crystal teaches "the applicability of antigen presenting cells, including dendritic cells . . . to treat cancer" by "transducing dendritic cells with dendritic cell-mediators, including CD40L and GM–CSF" to allow "CD40L to self-activate tumor antigen to $CD8^+$ CTL" (Ans. 3). The Examiner finds Crystal teaches "in vitro/ ex vivo manipulation of the dendritic cells" (*id.*).

The Examiner acknowledges that Crystal does not teach "a nucleotide compositions comprising a nucleotide sequence encoding a TAA and CpG in a vector and professional antigen-presenting cells / dendritic cells modified to express CD40L and/or GM-CSF" (Ans. 3).

The Examiner finds Hwu teaches "making recombinant antigen presenting dendritic cells . . . including transducing said cells with CD40 ligand GM-CSF . . . to produce highly potent antigen presenting cells that are capable of activating quiescent T cells and stimulate effective anti-tumor immune responses, including $CD8^+$ CTL" (Ans. 3).

The Examiner finds Krieg '067 teaches "immunomodulatory unmethylated CpG in vaccines" (Ans. 3). The Examiner finds Schetter teaches "the use of CpG nucleic acids in cancer vaccines, including professional antigen presenting cells/ dendritic cells" (*id.* 4).

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[15] Tanaka et al., *Generation of HLA-DRB1*1501-restricted p190 minor bcr-abl (ela2)-specific CD4 + T lymphocytes*, 109 Br. J. Haematology 435–7 (2000).

The Examiner finds Kung teaches "that TLR9 is critically involved in recognition by CpG motifs, that plasmacytoid dendritic cells express TLR9, that the CD40 pathway in addition to CpG played an important role in signaling pathways and immune responses" (Ans. 4). The Examiner similarly finds Hornung teaches "TLR9 is critical for recognition of CpG motifs" (*id.*). The Examiner also finds Krieg '680 teaches "the applicability of CpG to induce high levels of immune stimulation . . . including dendritic cells and the role of GM-CSF . . . to enhance immune responses, including cancer therapies and vaccines . . . which immune activation / stimulation relies upon TLR9" (*id.*).

The Examiner finds Fonteneau teaches the role of plasmacytoid dendritic cells in adaptive immunity and Pullarkat teaches "that human lymphoid dendritic cells activated with CD40L and influenza virus induced strong p-100 melanoma peptide-specific autologous CTL responses" (Ans. 4). The Examiner finds Brenner teaches "plasmacytoid dendritic cells and their use immune adjuvants in dendritic cell vaccines to elicit antitumor and antiviral immunity" (*id.* 5).

> The Examiner finds the ordinary artisan would have been motivated to provide nucleotide compositions comprising a nucleotide sequence encoding a TAA and CpG in a vector and professional antigen-presenting cells / dendritic cells, including TLR9 expressing plasmacytoid dendritic cells, modified to express CD40L and/or GM-CSF in composition form, consistent with the teachings of the prior art of combining such elements to achieve potent immunization against cancer/ tumor antigens, given the teachings . . . to enhance immune response to antigens, including cancer/ tumor antigens of interest.

(Ans. 5).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's finding that the prior art render the claims obvious?

Findings of Fact

1. Crystal teaches "a method of treating cancer in a mammal. This method comprises administering a dendritic cell-mediator to the mammal in combination with dendritic cells" (Crystal ¶ 71).

2. Crystal teaches that "[p]referably, the DC [dendritic cell] is modified in the context of the present inventive methods by contacting the DC with a nucleic acid molecule comprising a nucleic acid sequence encoding a dendritic cell-mediator" (Crystal ¶ 83).

3. Crystal teaches "[e]xamples of DC-mediators include . . . granulocyte-macrophage colony stimulating factor (GM-CSF) (Crystal ¶ 79).

4. Crystal teaches a "preferred dendritic cell-mediator that increases DC maturation is CD40 ligand (CD40L)" (Crystal ¶ 79).

5. Crystal teaches "[a]dministration to a mammal of a . . . modified dendritic cell that expresses a DC-mediator, alone or in further combination with an antigen" (Crystal ¶ 126).

6. Crystal teaches that "where the mammal has a cancer, the antigen is a cancer antigen" (Crystal ¶ 107).

7. Hwu teaches "new methods of making recombinant antigen presenting dendritic cells (DCs)"; that "recombinant cells expressing antigenic peptides were found to be competent to activate T-cells against target cells expressing selected antigens in vivo"; and that "[t]his provides powerful new treatments for cancers" (Hwu ¶ 7).

8. Hwu teaches "cytokine genes, such as GM-CSF can be introduced into dendritic cells, to potentially enhance their survival, immunogenicity or therapeutic effect. . . . Stimulatory ligands, such as CD40L, can be introduced in dendritic cells, to enhance their survival, immunogenicity or therapeutic effects" (Hwu ¶ 50).

Hwu also teaches tumor associated antigens, where "[e]xamples of MHC class I bound antigens include prostate specific antigen (PSA . . . Melanoma antigens (e.g. MAGE-1, MART-1 and gp 100), Colon cancer antigens (e.g., CEA), breast cancer antigens (e.g. HER-2)" (Hwu ¶ 54).

9. Hwu teaches "[d]endritic cells have been effective against established tumors. Dendritic cells have several advantages over other forms of anti-tumor immunization . . . dendritic cell immunizations can be used in combination with other methods of immunization" (Hwu ¶ 48).

10. Krieg '067 teaches that "DNA vaccine vectors can be improved . . . by the addition of CpG-S motifs" (Krieg '067 ¶ 28).

11. Krieg '067 teaches "an effective amount of a nucleic acid construct containing at least one unmethylated CpG for treating a disorder could be that amount necessary to induce an immune response of sufficient magnitude to eliminate a tumor, cancer, or bacterial, parasitic, viral or fungal infection" (Krieg '067 ¶ 62).

12. Schetter teaches "a dendritic cell vaccine which includes whole dendritic cells which have been exposed to a cancer antigen or a cancer-associated antigen in vitro" and explains that the "use of CpG-like nucleic acids in conjunction with cancer vaccines provides an improved antigen-specific humoral and cell-mediated immune response" (Schetter ¶¶ 276–277).

13. Hornung teaches "plasmacytoid dendritic cell (PDC) has been identified as a primary target cell for CpG ODN" (Hornung 4531, col. 1).

14. Hornung teaches that "TLR9 is essential for recognition of CpG ODN in mice and confers responsiveness to CpG ODN in human cell lines" (Hornung 4536, col. 1).

15. Krug teaches "TLR9, which is critically involved in the recognition of CpG motifs in mice, was present in PDC [plasmacytoid dendritic cells] but not in MDC [myeloid dendritic cells]. . . CpG ODN acts as an enhancer of T cell help, while T cell-controlled restriction to foreign antigens is maintained" (Krug, abstract).

16. Brenner teaches "there is great promise in the application of DCs [dendritic cells] as immune adjuvants for treating cancer" (Brenner 365, col. 2). Brenner further explains that "the BCR/ABL CML-specific gene products would serve as the ideal target antigen for adoptive immunotherapy" (Brenner 366, col. 2).

Principles of Law

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

Graham Factors

Level of Ordinary Skill in the Art

We note that the asserted prior art of record reflects a level of ordinary skill in the art that represents Ph.D. and/or M.D. scientists with several years of experience (*see, e.g.*, Hornung 4531, ft. 1 "This work is part of the

dissertation of V.H." and ft. 3 "Dr. Gunther Hartmann"; Brenner 356 "Malcolm Brenner M.D., Ph.D"). *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc*., 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

Scope and Content of the Prior Art[16]

Crystal teaches therapeutic cancer vaccine compositions that include two components: antigens (FF 5) and modified dendritic cells that express a dendritic cell mediator (FF 4–5) where the mediator may include GM-CSF (FF 2) and/or CD40 ligand (FF 3). Hwu teaches that reasons to incorporate tumor associated antigens as well as GM-CSF and CD40 ligand into dendritic cells for cancer vaccines include enhanced "survival, immunogenicity or therapeutic effects" (FF 8).

Crystal and Hwu do not teach CpG as the antigen in the cancer vaccine. Also, neither Crystal nor Hwu suggest which of the two types of dendritic cells should be used in the vaccine, plasmacytoid or myeloid.

Schetter teaches the "use of CpG-like nucleic acids in conjunction with cancer vaccines provides an improved antigen-specific humoral and cell-mediated immune response" (FF 12). Krieg '067 teaches an amount of "unmethylated CpG for treating a disorder could be that amount necessary to induce an immune response of sufficient magnitude to eliminate a tumor" (FF 11).

Hornung teaches "plasmacytoid dendritic cell (PDC) has been identified as a primary target cell for CpG" and that "TLR9 is essential for

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[16] We note the Board may rely on less than all of the references applied by the Examiner in an obviousness rationale without designating it as a new ground of rejection. *In re Bush*, 296 F.2d 491, 496 (CCPA 1961).

recognition of CpG ODN in mice and confers responsiveness to CpG ODN in human cell lines" (FF 13–14). Krug confirms that "TLR9, which is critically involved in the recognition of CpG motifs in mice, was present in PDC [plasmacytoid dendritic cells] but not in MDC [myeloid dendritic cells]" (FF 15).

Differences from Claimed Invention and the Prior Art

We recognize that Crystal does not anticipate the instant claims and that the cancer vaccine of Crystal differs from the cancer vaccine of the claimed invention by failing to specifically identify CpG as the antigen and plasmacytoid cells as the dendritic cells.

However, we agree with the Examiner that the ordinary artisan would have had reason to make a cancer vaccine that combined a CpG antigen of Schetter and Krieg '067 with the GM-CSF and/or CD40 ligand modified dendritic cells of Crystal and Hwu because: a) Crystal teaches that dendritic cell cancer vaccines may include antigens (FF 5); b) Schetter teaches that CpG used with cancer vaccines results in improved immune response (FF 12); and c) Krieg '067 teaches that CpG in appropriate doses helps mount an immune response sufficient to eliminate tumors and cancer (FF 11) (*see* Ans. 5).

We also agree with the Examiner that the ordinary artisan would have had reason to select plasmacytoid cells rather than myeloid cells for a cancer vaccine that combined CpG antigen and dendritic cells because Hornung teaches that plasmacytoid cells are the target of CpG and Krug teaches that the TLR9 component of plasmacytoid cells is critical for recognition of CpG and this TLR9 component is not found in myeloid dendritic cells (FF 13–15). Thus, the ordinary artisan, interested in a cancer vaccine that combined

dendritic cells and CpG, necessarily needed to select a type of dendritic cell that would interact with CpG. Krug evidences that only the plasmacytoid dendritic cells expressing TLR interact with CpG (FF 15), thus suggesting their use in vaccines that include CpG.

Secondary Considerations

Figure 15 of the Specification is reproduced below:

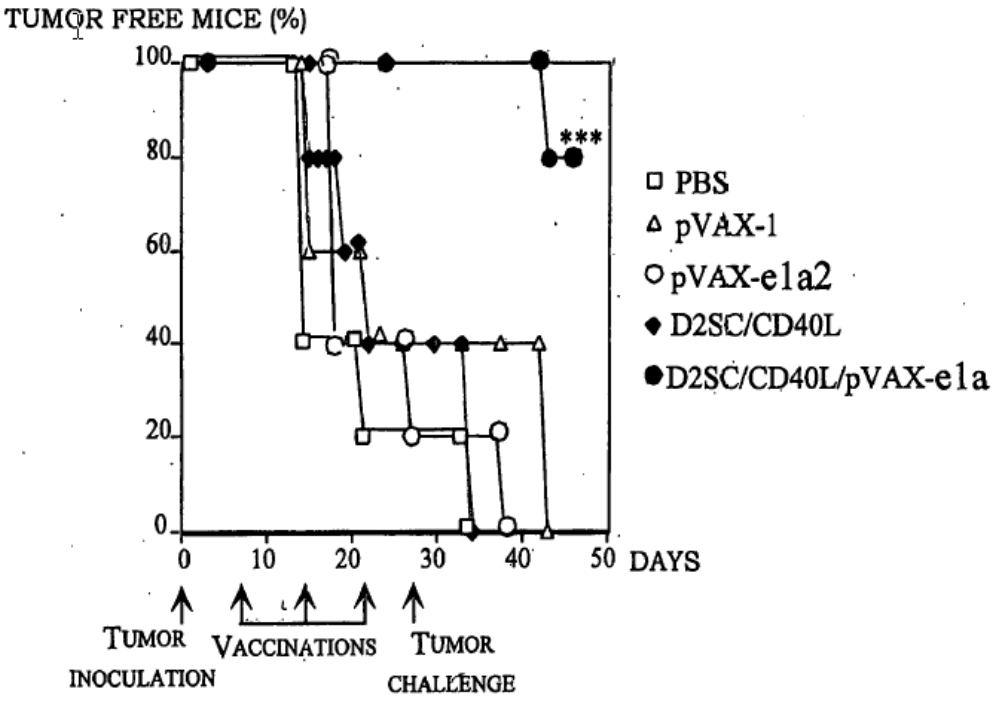

FIGURE 15

Figure 15 shows that tumor-bearing mice treated repeatedly with pVAXela2 and DC/CD40L develop efficient anti-tumor immunity sufficient to protect mice against rechallenge of tumor cells and approximately 80 % mice were protected and remained tumor free" (Spec. 36:32 to 37:3).

Appellant contends "neither the vector-contained nucleic acid component alone nor the antigen-presenting cells component alone provided

the efficient anti-tumor immunity of the claimed composition . . . Thus, the claimed combination provides a significant therapeutic improvement in cancer treatment over the individual components" (Appeal Br. 11). Appellant's position is supported by Dr. Morein,[17] who states "this vaccine formulation is surprisingly generating protective and therapeutic anti-tumor effects" (Morein Decl. ¶ 7). Dr. Morein further notes the "potent immune response evoked by the use of the combined vaccine composition is not proposed by the cited references and the vaccine of this invention cannot simply done by one skilled in the art without information from the present invention or being the inventor" (*id.*).

Analysis

Claim 75

We agree with the Examiner that the evidence of record, when considered as a whole, renders claim 75 obvious. We address Appellant's arguments below.

Appellant points to the data in the Specification and contends "these comparisons further demonstrate the surprising improvements of the claimed compositions and methods of the present invention" (Appeal Br. 12). Appellant contends "the improvement obtained by the present composition, comprising both the vector-contained nucleic acid component and the plasmacytoid dendritic cells modified for expression of CD40 ligand, is indeed surprising and anything but predictable from the results obtained by use of each component alone" (*id.* 13).

[17] Declaration of Dr. Bror Morein, dated Mar. 24, 2017.

As to claim 75, we find this argument unpersuasive, because the data in figures 15 and 17 of the Specification is solely drawn to cells with CD40 ligand and solely to the use of the e1a2 tumor associated antigen, and does not demonstrate any result for cells with GM-CSF or with any other tumor antigens.[18] Thus, the results are not commensurate with the scope of claim 75 which requires only "at least one of CD40 Ligand and GM-CSF" and "a tumor associated antigen" and does not necessarily require CD40 Ligand or the specific e1a2 tumor antigen tested. Unexpected results must be "commensurate in scope with the degree of protection sought by the claimed subject matter." *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005).

Appellant contends

> the rejection fails to provide any apparent reasoning that would motivate one of ordinary skill in the art to select and combine all the teachings of the various cited references along the lines of the composition of claim 75 and the method of claim 86, as opposed, for example, along the lines of the comparative compositions (d)-(g) noted above with respect to Fig. 17.

(Appeal Br. 12; *cf.* Appeal Br. 13).

We find this argument unpersuasive because, as discussed above, we agree with the Examiner that the ordinary artisan would have had reason to incorporate GM-CSF and CD-40 ligand into the cancer vaccine of Crystal

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[18] We note the Specification lists a variety of antigens, teaching: "Non-limiting examples of tumor-specific or tumor-associated antigens, the coding sequence of which may be used in the vaccine composition of the invention, include KS 1/4 pan-carcinoma antigen, ovarian carcinoma antigen (CA125), prostatic acid phosphate, prostate specific antigen, melanoma-associated antigen p97, melanoma antigen gp75, high molecular weight melanoma antigen, the MAGE family of antigens, T cell receptor γ chain alternate reading frame protein (TARP) antigen, prostate specific membrane antigen and ela2 fusion protein antigen and bcr/abl fusion protein" (Spec. 20:12–20).

because Hwu teaches these result in enhanced "survival, immunogenicity or therapeutic effects" (FF 8). Further, Crystal teaches the use of an antigen (FF 5) and Schetter and Krieg teach CpG is an antigen that improves cancer vaccines (FF 10–11).

Appellant specifically contends that "none of these references would have given one of ordinary skill in the art any apparent reason to employ dendritic cells expressing TLR9 in Crystal, or any reasonable expectation of success in doing so" (Appeal Br. 14). Appellant further contends:

> neither Krug nor Hornung provides any teaching of plasmacytoid dendritic cells modified for stable expression of CD40 ligand or GM-CSF as required by claims 75 and 86. Neither of these references provide one of ordinary skill in the art with any reason to employ plasmacytoid dendritic cells expressing TLR9 in the method of Crystal, and therefore one of ordinary skill in the art could not have had any reasonable expectation from these references of success by using plasmacytoid dendritic cells expressing TLR9, modified to express CD40 ligand or GM-CSF, in the method of Crystal.

(Appeal Br. 15).

We are not persuaded because we agree with the Examiner that the ordinary artisan, taught by Crystal to use dendritic cells (FF 1), would have selected plasmacytoid dendritic cells rather than myeloid dendritic cells, from the two known types of dendritic cells, because Hornung teaches that plasmacytoid cells are the target of CpG and Krug teaches that the TLR9 component of plasmacytoid cells is critical for recognition of CpG and this TLR9 component is not found in myeloid dendritic cells (FF 13–15). Hornung and Krug provide evidence that one would expect greater success with plasmacytoid cells that express TLR9 rather than myeloid dendritic cells because CpG would be expected to function as an "enhancer of T cell

help" in the plasmacytoid dendritic cells (FF 15). "Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

Appellant then separately argues that Hwu and Schultze do not teach the claimed invention (*see* Appeal Br. 16); that Schetter does not teach the use of plasmacytoid dendritic cells (*id.*); and that Fonteneau, Pullarkat, and Brenner also don't provide reasons to select plasmacytoid dendritic cells (*id.* 17–18).

While we do not rely on Fonteneau, Pullarkat, and Brenner, we find these arguments unpersuasive generally because "the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference . . . Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). For the reasons already given above, we agree with the Examiner that the ordinary artisan would have had reason to use plasmacytoid cells that inherently express TLR9 in the cancer vaccine of Crystal with CpG as the antigen (FF 1–15).

Appellant relies on the Morein Declaration, asserting that "Dr. Morein notes that he does not find any information from Crystal, Hwu, Kreig, or Hornung for using plasmacytoid dendritic cells to efficiently treat a tumor and to induce tumor-specific immune response" (Appeal Br. 19–20). Specifically, Dr. Morein states:

> As one skilled in the art, I do not find any information in the studies from the following publications; Crystal et al, US 2003/0202963 Al, Hwu et al, US 2004/0146492 Al, Kreig et al,

> US 2004/0186067 Al, Hornung et al, J lmmunol., 168:4531-4537 (2002) (Hornung), that can be related to and relevantly oppose to the present vaccine formulation of using the plasmacytoid dendritic cells to efficiently be used for treating tumor and to inducing tumor-specific immune responses.

(Morein Decl. ¶ 4).

We find Dr. Morein's conclusory statement unpersuasive because Dr. Morein does not persuasively explain why the combination of teachings of Hornung and Krug do not suggest using plasmacytoid dendritic cells when following Krieg and Schetter's guidance to use the CpG antigen in cancer vaccines (FF 10–12). When CpG is the antigen of interest, Krug teaches "TLR9, which is critically involved in the recognition of CpG motifs in mice, was present in PDC [plasmacytoid dendritic cells] but not in MDC [myeloid dendritic cells]" (FF 15). This is a direct teaching that CpG will only function with plasmacytoid cells and not myeloid cells, reasonably suggesting to the ordinary artisan, interested in the enhanced immune response provided by CpG, to select plasmacytoid dendritic cells rather than myeloid dendritic cells. Hornung reinforces that point in teaching "plasmacytoid dendritic cell (PDC) has been identified as a primary target cell for CpG ODN" (FF 13).

We find the absence of reasoning significantly weakens the persuasive power of Dr. Morein's position. "[T]he PTAB is permitted to weigh expert testimony and other record evidence and, in so doing, rely on certain portions of an expert's declaration while disregarding others." *Icon Health and Fitness, Inc. v. Strava, Inc*., 849 F.3d 1034, 1041 (Fed. Cir. 2017). *See In re American Academy of Science Tech Center*, 367 F.3d 1359, 1370 (Fed.

Cir. 2004) ("[T]he Board is entitled to give such weight to declarations as it deems appropriate.")

Claim 92

Appellant separately contends that "one of ordinary skill in the art would not have had any reasonable expectation of the significant therapeutic improvement in cancer tumor treatment provided by the composition of claim 92" (Appeal Br. 24).

We find this argument unpersuasive for the same reasons as given above. While the Specification does provide data of superior results for a composition comprising the specific CD40 ligand and e1a2 antigen (*see* Spec. Fig. 15) and claim 92 is limited to CD40 ligand, claim 92 is not limited to the e1a2 peptide that was tested. The evidence of record does not demonstrate that the result for the particular e1a2 tumor associated antigen would necessarily occur using other tumor associated antigens, such as those disclosed by Hwu for use in a dendritic cell cancer vaccine (FF 8) and therefore the results in Figure 15 of the Specification are not commensurate in scope with claim 92. *Harris*, 409 F.3d at 1344.

Claim 95

Appellant contends

> the Official Action does not indicate where in any of the references plasmacytoid dendritic cells expressing TLR9, CD8α+ and B220+ are modified for stable expression of CD40 ligand encoded by a nucleotide sequence engineered into the cells, particularly with any suggestion to combine and incubate such modified cells with a nucleic acid provided in a plasma vector as required by claim 95.

(Appeal Br. 25).

We find this argument persuasive based on the recitation of TLR9, CD8α+ and B220+ in claim 95. While Krug reasonably evidences that plasmacytoid cells inherently comprise TLR9 (FF 13), the Examiner has not provided a persuasive reason to include the CD8α+ and B220+ in the plasmacytoid dendritic cells nor has the Examiner established that these antigens are inherently naturally expressed by plasmacytoid dendritic cells. To the extent that Fonteneau teaches that the immune response to influenza involves CD8α+ and B220+ antigens, we are not persuaded that this is relevant. We therefore agree with Appellants that Examiner has provided no persuasive reason to generate the modified dendritic cell required by the cancer vaccine of claim 95.

Claims 76 and 87

Appellant contends

> the Official Action does not indicate where in any of the references one of ordinary skill in the art would find a reason to incubate plasmacytoid dendritic cells modified for stable expression of CD40 ligand encoded by a nucleotide sequence engineered into the cells with a nucleic acid provided in a plasma vector as required by claims 76 and 87.

(Appeal Br. 26).

We find this argument unpersuasive because we agree with the Examiner that "pre-incubated combined mixture of said nucleic acids and said modified antigen-presenting cells would have been a necessary or obvious step in combining the nucleic acids and antigen presenting cells" (Ans. 23). We also note that Crystal teaching of administration of "a modified dendritic cell that expresses a DC-mediator . . . in further combination with an antigen" (FF 5) reasonably suggests that the

components are mixed together prior to administration.

Claim 82

Appellant contends that "the experimental showings in the specification are specifically representative of the composition of claim 82 wherein the plasmacytoid dendritic cells are modified for stable expression of CD40 ligand" (Appeal Br. 26).

We find this argument unpersuasive for the reasons already given. In particular, while claim 82 recites CD40 ligand, claim 82 is inclusive of any antigen, not just the e1a2 antigen tested in figures 15 and 17. Therefore, claim 82 is not commensurate in scope of the argued results. *Harris*, 409 F.3d at 1344.

Claims 83–85, 91, 93

Appellant contends

> neither Ni nor Tanaka teach or suggest a therapeutic composition including a nucleic acid as required by any of claims 83-85, 91 and 93 in combination with plasmacytoid dendritic cells modified to express CD40 ligand or GM-CSF or the significant therapeutic effect obtained by such a combination. That the e1a peptide or *bcr-abl* fusion protein antigen are known does not resolve the deficiencies of the remaining references in failing to lead one of ordinary skill in the art to the claimed combinations with a reasonable expectation of the significant therapeutic improvement provide by the claimed compositions as demonstrated in the present specification.

(Appeal Br. 33).

We begin by noting that SEQ ID NO: 5 is "referred to as ela2 peptide" (Spec. 26:28) and that claim 83 is limited to SEQ ID NO: 5, but depends from claim 75 and therefore is not limited to the CD40 ligand. Claims 84 and 85, drawn to other e1a2 fusion proteins (*see* Spec 31:32),

similarly depend from claim 75 and are not limited to the CD40 ligand. Claim 91 is more broadly drawn to any bcr-abl fusion protein, depends from claim 75, and therefore is not limited to either the CD40 ligand or the e1a2 tumor associated antigen tested. While claim 93 depends from claim 92, and therefore is limited to the CD40 ligand, claim 93 broadly encompasses either a bcr-abl fusion protein or the specific tested e1a2 fusion peptide. Claim 93 is therefore not limited to the specific tumor associated antigen demonstrated in the results. Therefore, claims 83–85, 91, and 93 are not commensurate in scope of the argued results. *Harris*, 409 F.3d at 1344.

Claims 94 and 97

Having found claim 95 unobvious for the reasons given above, we also find dependent claim 97 unobvious for the same reasons.

As to claim 94, Appellant contends "the evidence of record simply fails to teach that the art recognizes that any combination of known elements in a mixture achieves such potent immunization against cancer/tumor antigen as demonstrated in the present application" (Appeal Br. 35).

We find this argument unpersuasive for the reasons already given. In particular, while claim 94 recites an improved tumor killing result by the combination of the CpG and modified plasmacytoid dendritic cell, claim 94 is inclusive of any antigen, not just the e1a2 antigen tested in figures 15 and 17. Therefore, claim 82 is not commensurate in scope of the argued results. *Harris*, 409 F.3d at 1344. In addition, Krieg provides evidence that vaccines, and cancer vaccines in particular, are improved by including CpG (FF 10). Indeed, Schetter specifically states that the "use of CpG-like nucleic acids in conjunction with cancer vaccines provides an improved antigen-specific humoral and cell-mediated immune response" (FF 12).

This supports the conclusion that the result of claim 94 is an expected, not unexpected result.

Claim 96

Having found claim 95 unobvious for the reasons given above, we also find dependent claim 96 unobvious for the same reasons.

Conclusion of Law

Except as otherwise noted above regarding claims 95–97, the evidence of record supports the Examiner's finding that the prior art renders the claims obvious.

DECISION

In summary:

Claims Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
75, 76, 79–89, 91–97	103(a)	Crystal, Hwu, Krieg '067, Schetter, Schultze, Krug, Hornung, Krieg '680, Fonteneau, Pullarkat, Brenner	75, 76, 79–89, 91–94	95–97
75, 76, 79–89, 91–97	103(a)	Crystal, Hwu, Krieg '067, Schetter, Schultze, Krug, Hornung, Krieg '680, Fonteneau, Pullarkat, Brenner, Ni, Tanaka	75, 76, 79–89, 91–94	95–97
Overall Outcome			75, 76, 79–89, 91–94	95–97

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-IN-PART