NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

2008-1119
(Serial No. 10/041,958)

IN RE SAUL TZIPORI, RAMASWAMY BALAKRISHNAN,
and ARTHUR DONOHUE-ROLFE

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences.

DECIDED: October 15, 2008

Before MICHEL, Chief Judge, FRIEDMAN, Circuit Judge, and WALKER,[*] Chief District Judge.

MICHEL, Chief Judge.

Appellants Saul Tzipori, Ramaswamy Balakrishnan, and Arthur Donohue-Rolfe (collectively "Tzipori") appeal the determination of the Board of Patent Appeals and Interferences ("Board") that the invention of all claims of their patent application, No. 10/041,958 ("the '958 application"), would have been obvious under 35 U.S.C. § 103(a) in light of a combination of five prior art references.

The claims on appeal are directed to antibodies which bind one subunit of Shiga-like toxin II ("SLT-II") and prevent or treat hemolytic uremic syndrome in people. The examiner rejected the claims as obvious in light of a combination of five prior art

[*] Honorable Vaughn R. Walker, Chief Judge, United States District Court for the Northern District of California, sitting by designation.

references. The Board affirmed the rejection. Tzipori appeals, arguing that (1) the Board erroneously failed to consider his claims individually, and (2) the invention of his claims would not have been obvious in light of the references cited by the examiner.

Because the Board (1) properly considered Tzipori's claims in groups, and (2) applied the correct legal standard for obviousness and reached a decision supported by substantial evidence, we affirm.

I. BACKGROUND

A. Antibodies and Shiga-Like Toxin II

Antibodies are molecules central to the operation of the immune system. Antibodies bind to antigens, i.e., substances in a body that the body considers foreign. The binding portion of an antibody is complementary in shape and charge to the portion of the antigen to which the antibody binds. Antibodies have been used to develop treatments for various diseases.

Escherichia coli ("E. coli") is a common bacterium that often lives in the intestinal tract of a variety of mammals, including humans. Some E. coli secrete SLT-II, which then can cause damage independently of the E. coli bacterium. E. coli that produce SLT-II can live in a variety of different animals, but SLT-II-producing E. coli have a more detrimental effect on some animals than on others.

SLT-II-producing E. coli make holes in the intestines of humans and pigs, but not other animals. These intestinal holes allow SLT-II to pass out of human and pig intestines and into systemic circulation, making SLT-II particularly dangerous to pigs and humans. In humans, SLT-II-producing E. coli can cause hemolytic uremic syndrome, a disease which is fatal in some cases.

B. The '958 Application

Tzipori infected young pigs with SLT-II-producing E. coli and used them to estimate effective doses of antibodies to SLT-II. In the '958 application, Tzipori claims antibodies to SLT-II, which, if injected into a person, could bind to SLT-II and ameliorate its harmful effects. The only independent claim at issue on appeal, claim 26, reads:

> A dosage formulation comprising an effective amount of human or humanized monoclonal antibodies, the antibodies consisting of antibodies neutralizing Shiga like toxin II in vivo wherein the antibodies are specifically reactive with a single subunit of the Shiga like toxin II produce[d] by Escherichia coli which causes hemolytic uremic syndrome to prevent or treat hemolytic uremic syndrome in a human.

At issue on appeal are also several dependent claims of claim 26. They add limitations such as that the antibodies must be made using recombinant DNA technology (claim 28), bind to the alpha subunit of SLT-II (claim 30), or be effective to treat listed neurological symptoms (claim 31).

Citing two patents, one patent application, and two scientific journal articles, the examiner rejected all pending claims of the '958 application as obvious. Tzipori appealed these rejections to the Board, which affirmed the examiner's rejections. Tzipori now appeals to this court.

II. DISCUSSION

In its decision, the Board considered only claims it deemed representative: claims 26, 28, 30, 31, and 32. The Board found the invention embodied in each of these five claims obvious in light of prior art.

A. Grouping of Claims

Tzipori argues that the Board erred in considering certain of his claims together. Although Tzipori stated in his substitute appeal brief to the Board that "[t]he claims do

not stand or fall together," he organized his claims into four groups: (a) 27 through 29, (b) 30 and 33, (c) 31, and (d) 32, and 34 through 36. Tzipori did not separately argue for the allowability of his only independent claim, claim 26. The Board nonetheless considered claim 26 as a fifth claim group.

Tzipori points to no part of the record in which he made arguments specific to only one claim of a multi-claim group. Tzipori instead appears to have argued his claims as he grouped them. For example, to the Board, Tzipori argued:

> The prior art does not teach administration of humanized (claim 27), recombinant (claim 28) or chimeric humanized antibodies (claim 29). The examiner has used hindsight to say that it would be obvious to substitute humanized, recombinant or chimeric antibodies for the antibodies described by Krivan or Williams.

Even on appeal to this court, Tzipori generally argues his claims in the same groups he delinated for the Board.

Tzipori's statement in his appeal brief that the claims do not stand or fall together, followed by four groupings of claims and arguments directed to those claims as groups, is insufficient to require the Board to give individual consideration to each of Tzipori's claims. The applicable regulation, which Tzipori does not challenge, requires an applicant to clearly identify and separately argue those claims for which he requests the Board's specific attention. See 37 C.F.R. § 41.37.[1] If an applicant does not comply

[1] Title 37 C.F.R. § 41.37 provides, in part:

> For each ground of rejection applying to two or more claims, the claims may be argued separately or as a group. When multiple claims subject to the same ground of rejection are argued as a group by appellant, the Board may select a single claim from the group of claims that are argued together to decide the appeal with respect to the group of claims as to the ground of rejection on the basis of the selected claim alone. Notwithstanding any other provision of this paragraph, the failure of

with this regulation, the Board "is free to select a single claim from each group of claims subject to a common ground of rejection as representative of all claims in that group and to decide the appeal of that rejection based solely on the selected representative claim." In re McDaniel, 293 F.3d 1379, 1383 (Fed. Cir. 2002). The Board did not err in considering Tzipori's claims in the very groups he himself argued to the Board.

B. Obviousness

Obviousness is a question of law based on underlying questions of fact. Winner Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1348 (Fed. Cir. 2000). The underlying factual inquiries in an obviousness analysis "include 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) evidence of secondary factors, also known as objective indicia of non-obviousness." Eisai Co. v. Dr. Reddy's Labs., 533 F.3d 1353, 1356 (Fed. Cir. 2008).

The Board affirmed the examiner's rejection of claim 26 as obvious in light of references which the parties refer to as Krivan,[2] Queen,[3] Perera,[4] Williams,[5] and Engleman.[6] Krivan is the primary reference of this obviousness rejection.

> appellant to separately argue claims which appellant has grouped together shall constitute a waiver of any argument that the Board must consider the patentability of any grouped claim separately. Any claim argued separately should be placed under a subheading identifying the claim by number. Claims argued as a group should be placed under a subheading identifying the claims by number. A statement which merely points out what a claim recites will not be considered an argument for separate patentability of the claim.

[2] U.S. Patent No. 5,512,282 to Krivan et al.

[3] Published Patent Cooperation Treaty Application No. WO 90/07861 to Queen et al.

1. Claim 26

Although in his appeal brief to the Board Tzipori did not state that claim 26 should be considered separately, the Board nonetheless gave it individual consideration, presumably because it is the independent claim from which all of Tzipori's other claims depend.

a. Disclosure of Krivan

On appeal, Tzipori argues against this obviousness rejection primarily by praising aspects of his research that do not figure into the claims at issue, such as his research with gnotobiotic[7] piglets and his alleged discovery that SLT-II-producing E. coli only form lesions in the intestines of humans and pigs, not other animals. However, Tzipori's criticism of the prior art for failing to reveal this is, at times, equally applicable to his own claims. For example, he states:

> Krivan describes animal antibodies to SLTs generally, without identifying or disclosing which SLT is the one that causes HUS in humans. There is

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[4] L.P. Perara, L.R.M. Marques, A.D. O'Brien, "Isolation and Characterization of Monoclonal Antibodies to Shiga-Like Toxin II of Enterohemorrhagic Escherichia coli and Use of the Monoclonal Antibodies in a Colony Enzyme-Linked Immunosorbent Assay," 26(10) J. Clin. Microbio. 2127-2131 (1988).

[5] U.S. Patent No. 6,080,400 to Williams et al.

[6] Danuta Kozbor & Carlo M. Croce, "Human lymphoblastoid Cell Lines as Fusion Partners," in Human Hybridomas and Monoclonal Antibodies 22-27 (Edgar G. Engleman et al., eds. 1985).

[7] The parties do not define gnotobiotic, although Tzipori indicates that gnotobiotic piglets do not receive antibodies from their mothers' milk. The Oxford English Dictionary (2d ed. 1989) defines gnotobiotic as "Of an organism (esp. a higher animal) or its environment: artificially rendered devoid of bacteria and other organisms which would normally be present as parasites, commensals, symbionts, etc., or having only a few known organisms of this kind present." Precisely what Tzipori means by gnotobiotic in the '958 application, however, is not germane to the outcome of this appeal.

> no disclosure of the relevant subunits to that specific SLT, nor how those subunits are responsible for the enteric and systemic disease in humans.

Krivan discloses that SLT-II existed and that it had subunits. Krivan at 2:14-17; 16:14-17; 17:60-62. Krivan discloses purifying SLT-II and using it to make polyclonal bovine antibodies to SLT-II, but does not specify that these antibodies bind specifically to one subunit or the other of SLT-II. Id. at 15:36-43. Krivan did, however, note that "a subunit of one or more of the toxins can be used" to manufacture antibodies, id. at 8:54-60, which one of ordinary skill in the art would readily understand would produce antibodies specific to that subunit.[8]

Tzipori's claim 26 involves antibodies directed to "a single subunit of" SLT-II. Dependent claims 30 and 33 are limited to antibodies binding the alpha and beta subunits, respectively, of SLT-II. However, as these are, according to Tzipori, the only subunits of SLT-II, his implication that his claims are patentable because they are limited to the subunits "responsible for the enteric and systemic disease in humans" rings hollow. Tzipori's claims are, as a whole, directed to all parts of SLT-II and no more specific than Krivan's disclosure on this point.

Tzipori also asserts that his gnotobiotic pig model is novel and renders his claims patentable over the prior art. In support of this argument, Tzipori offers declarations of several researchers extolling the virtues of the gnotobiotic pig model. It is, however, Tzipori's claims—not his specification—that are the focus of an obviousness inquiry.

[8] Additionally, Perera recites that "[a]ll the neutralizing MAbs [i.e., monoclonal antibodies] generated in the present study recognized the A subunit of SLT-II." Perera at 2130.

See MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1366 (Fed. Cir. 1999). His gnotobiotic pig model is therefore of little relevance to the obviousness inquiry.[9]

Tzipori also argues that

> [a]n important aspect of the studies conducted by Tzipori was the use of a virulent strain of E. coli (the 0157:H7 strain) that infects and causes disease in humans. Krivan does not recognize that the strains of E. coli infect different hosts differently, and therefore that one cannot extrapolate from therapeutics in one species, such as cattle, for use in humans, even though the organism, E. coli, is the same, because there are differences in the toxins different strains produce, and between the host species, which are infected differently and have different diseases.

Krivan, however, did recognize that differences existed among various strains of SLT-producing E. coli: "The SLT-producing E. coli is a heterogeneous group of bacteria that belong to several different O:H:K serotypes, but they all have in common the ability to discharge one or more SLTs." Krivan at 1:43-46. Krivan also observed that "SLT-producing E. coli cause a spectrum of diseases in humans from mild, uncomplicated diarrhea and bloody diarrhea to two life-threatening complications, hemorrhagic colitis and hemolytic uremic syndrome (HUS)." Id. at 1:46-50. The Krivan patent recited that one object of its invention was "to provide pharmaceutical compositions for the prevention, amelioration, or treatment of disease in a human or animal caused by an SLT." Id. at 6:3-6.

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[9] Furthermore, the Director questions the novelty of the gnotobiotic pig model. He points out that the declaration of Dr. Florian Gunzer—which Tzipori submitted during prosecution—indicates that Gunzer has "worked since 1994 with the swine model for human infection with enteric pathogens." The Director also calls attention to an article published in 1989 entitled "Nature and distribution of mucosal lesions associated with enteropathogenic and enterohemorrhagic Escherichia coli in piglets and the role of plasmid-mediated factors." Tzipori asserts the '958 application is entitled to a priority date of November 15, 1996. However, because Tzipori's claims do not cover the gnotobiotic pig model, we need not decide whether these two references disclose it.

Again, Tzipori's claims are no more specific than Krivan's patent on this point. Tzipori merely claims antibodies against "a single subunit of the Shiga like toxin II produce[d] by Escherichia coli which causes hemolytic uremic syndrome to prevent or treat hemolytic uremic syndrome in a human." His claims do not specify that the antibodies bind specifically to SLT-II from the 0157:H7 strain of E. coli,[10] nor do they make clear how or whether the claimed antibodies differ from antibodies, such as those claimed by Krivan, which would be suitable for animal treatment.

Furthermore, as the Director points out, Krivan discloses that in cows, SLTs do not cause the ill effects that they do in humans. Krivan at 8:11-14. And Williams recognizes different strains of E. coli infect hosts differently. Williams contains a table dividing various E. coli strains into four different categories: enterotoxigenic, enteropathogenic, enteroinvasive, and verotoxin-producing. Williams, Table 1. Tzipori is incorrect that the prior art does not disclose that different strains of E. coli infect different hosts differently.

Tzipori argues that "there is no teaching in Krivan of the need in treating humans to make human or humanized antibodies to SLT II." However, Tzipori appears to conflate using human(ized) antibodies with using antibodies to treat disease in humans. Human antibodies are antibodies made by humans. And while there may be reasons to

[10] Even if Tzipori's claims were limited to antibodies against SLT-II made by the O157:H7 strain, it does not appear that using this strain for research was novel. Among the cited references in Perera are a pair entitled "Two toxin-converting phages from Escherichia coli O157:H7 strain 933 encode antigenically distinct toxins with similar biological activities" and "Purification and some properties of a Verotoxin from Escherichia coli O157:H7 that is immunologically unrelated to Shiga toxin." Perera at 2131. Other scientists in this field clearly used the O157:H7 strain in research. The table in Williams dividing E. coli strains into four categories places strain O157:H7 into the "verotoxin-producing" category. Williams, Table 1.

prefer human antibodies for human treatment, Tzipori has not proven that non-human antibodies are necessarily ineffective for human treatment. Krivan notes that "bovine IgG1 antibodies are relatively protease-resistant and highly homologous with human immunoglobulin G." Krivan at 3:32-34. And, as shown by claims 1, 17, and 18, Krivan claims bovine antibodies to SLT-II effective for treatment and prevention of human disease:

> **1.** Purified IgG, comprising high titer, monospecific polyclonal antibodies to Shiga-like toxin (SLT) obtained by a process comprising the steps of:
>
> inoculating a bovine animal with a purified, active SLT, derived from E. coli and selected from the group consisting of SLT I, SLT II, SLT IIV and mixtures thereof; and
>
> recovering and purifying IgG from said animal after said animal has had an immune response to said purified active SLT.
>
> . . .
>
> **17.** A method for the passive immunization of a human or animal against SLT toxemia comprising administering to said human or animal a prophylactically effective amount of the purified IgG of claim 1 to prevent said toxemia.
>
> **18.** A method for the treatment of SLT toxemia in a human or animal comprising administering a therapeutically effective amount of the purified IgG of claim 1 to treat said toxemia to said human or animal.

Krivan's claims are presumed enabled, Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1355 (Fed. Cir. 2003), and Tzipori has not proven that they are not.

Tzipori does point out correctly that two aspects of claim 26 are not present in Krivan, namely, that the antibodies are "monoclonal" and "human or humanized." Krivan instead discloses "monospecific, purified polyclonal antibodies." See, e.g., Krivan at 1:10-12. And rather than human or humanized antibodies, Krivan discloses

bovine antibodies. Id. at 15:30-19:16. Krivan thus contains disclosure corresponding to all aspects of Tzipori's claim 26 except "monoclonal" antibodies and "human or humanized" antibodies.[11]

b. Disclosure of Queen

Tzipori admits that Queen discloses a method of making humanized antibodies. See, e.g., Queen at 5:8-31, 6:21-25 ("When combined into an intact antibody, the humanized light and heavy chains of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen . . ."). Tzipori instead argues that "[t]hese techniques do not incorporate the use of an intact immune system to produce such humanized monoclonal antibodies." Tzipori does not explain why this is relevant; claim 26 does not require the antibodies be produced by an intact immune system. Given that the Board stated that the point of this argument of Tzipori's was "less than clear," we would have expected him to attempt to elucidate the issue on appeal. He has not, and we, like the Board, cannot accept the argument. Queen thus discloses one of the limitations of claim 26—"human or humanized antibodies"—not disclosed by Krivan.

c. Engleman

The Board mentioned in passing Engleman but did not discuss this reference in detail. Although the Board recited that "the evidence on this record weighs in favor of the Examiner's conclusion that claim 26 is prima facie obvious over the combination of

[11] The precise distinction between monoclonal antibodies and monospecific polyclonal antibodies is not critical to this appeal. For simplicity, we merely note that a group of monoclonal antibodies all bind to the same portion of the same antigen (and are identical), while a group of monospecific polyclonal antibodies all bind to different portions of the same antigen (and are not identical to each other).

Krivan, Perera, Williams, Queen and Engelman [sic]," it does not appear that the Board actually relied on Engleman in upholding the obviousness rejection of claim 26. The content of Engleman is not pertinent to whether the invention of claim 26 would have been obvious, and that the Board mentioned it is harmless.[12]

d. Disclosure of Perera

Perera discloses the manufacture of murine hybridomas that made "monoclonal antibodies" which "immunoprecipitated the isolated A subunit of SLT-II but not the B subunit." Perera at 2127. The E. coli strains that were the basis of the work in Perera were collected from "humans with diarrhea, hemorrhagic colitis, or hemolytic-uremic syndrome, calves with diarrhea, and pigs with edema disease." Id. Perera also described these antibodies as "neutralizing." Id. at 2130. Perera thus discloses the other limitation of claim 26—monoclonal antibodies—absent from Krivan.

e. Disclosure of Williams

The abstract of Williams begins, "[t]he present invention includes methods for generating neutralizing antitoxin directed against verotoxins." '400 Pat. at [57]. Williams further recites that "[t]hese antitoxins are useful in the treatment of humans and other animals intoxicated with at least one bacterial toxin, as well as for preventive treatment." Id. The disclosure of Williams is cumulative of references already discussed.

f. Combination of References

"The combination of familiar elements according to known methods is likely"—although not certain—"to be obvious when it does no more than yield predictable

[12] Engleman recounts the manufacture of a number of prior immunoglobulin-secreting human-human hybridomas. Engleman at 23-27.

results." KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007). The level of skill in the art is important to obviousness analysis because a more skilled artisan will have more general knowledge on which to rely in combining teachings from multiple references. See DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1370 (Fed. Cir. 2006). Tzipori admits that the ordinary level of skill in the art is high, that of one with both (1) a doctorate or medical degree, and (2) "experience in the treatment or research in infectious disease."

All art cited by the Board discusses making antibodies to SLT-II, and each of the individual limitations of claim 26 were known to those of skill in the art at the time Tzipori filed the '958 application. Tzipori argues that one of ordinary skill in the art would not combine the teachings of the references because some of the references, such as Williams, are directed to using antibodies to detect SLT-II-producing E. coli, not treating infection by SLT-II-producing E. coli. The Board stated that combining Krivan, Queen, Williams, Perera, and Engleman would have been obvious to one of ordinary skill in the art (as did the examiner[13]). The Board explained that a person of ordinary skill would have been motivated to combine "Perera's antibodies, which are capable of neutralizing the toxicity of the SLT II toxin" with the teachings of Krivan because the combination would result in a more effective therapy. The Board merely stated that the "substantially decreased immunogenicity" of Queen's method of humanizing antibodies would have motivated the combination with Krivan. It appears that the Board believed one of skill in

[13] Many documents, including the examiner's final rejection of Tzipori's claims, do not appear in the parties' joint appendix despite being listed in its table of contents. A portion of the examiner's answer to the Board, however, does appear in the joint appendix.

the art would combine Krivan and Williams because both references discussed treating human disease with antibodies to SLT-II.

The explanation of why one of ordinary skill in the art would combine the references cited by the examiner is one portion of the Board's decision where an elaboration of its reasoning would have been helpful to our review. For example, the Board stated

> [W]hen Perera is considered in the context of the combination of prior art relied upon by the Examiner, we find that a person of ordinary skill in the art would have understood that Perera's antibodies, which are capable of neutralizing the toxicity of the SLT II toxin, would be useful in the method taught by Krivan, as would human or humanized variants of Perera's antibodies.
>
> Accordingly, we are not persuaded by Appellants' intimation that simply because Perera does not teach a therapeutic use for his antibodies, a person of ordinary skill in the art would not understand Perera's contribution to the combination of references relied upon.

This, however, is little more than a verbose statement that Krivan and Perera reasonably would have been combined by one of ordinary skill in the art. The Board offered no facts or reasoning in support of this assertion. Our own review of the references leads us to believe the Board was correct, but we are not insensitive to Tzipori's charge that the Board decision is not based so much on stated reasoning as "a haze of so-called expertise."

Different situations require different approaches to the issue of obviousness; the Supreme Court takes an "expansive and flexible approach" to obviousness. KSR, 127 S. Ct. at 1739. "To facilitate review, this [obviousness] analysis should be made explicit." Id. at 1741; see also In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."). For example, we note that Krivan and Perera both

cite papers by people with the surnames of Karmali and Donoue-Rolfe,[14] which could be taken as evidence that researchers in Krivan's field would consult sources in Perera's field and vice versa (or that Krivan and Perera come from the same field). See Commonwealth Scientific & Indus. Research Org. v. Buffalo Tech. (USA) Inc., __ F.3d __, slip op. at 10 (Fed. Cir. Sept. 19, 2008) (Citation of one reference to another may "provide a justification for combining the references for obviousness purposes.") Alternatively, the Board could have shown that antibodies manufactured for one purpose can be used later for another. See In re ICON Health & Fitness, 496 F.3d 1374, 1379-80 (Fed. Cir. 2007) (Folding mechanism of bed could be used in combination to find folding treadmill obvious.).

We do not intend to give a definitive list of factors to consider, or mandate a rigid form of analysis to be used in all cases. We do, however, encourage the Board to explore the "flexible approach" to obviousness and to provide its reasoning in writing. Given the complexity of the technological issues and the combination of multiple references used to reject claim 26, a more comprehensive explanation of the Board's reasoning would have facilitated review not only by better presenting the Board's reasoning to this court, but also by giving Tzipori a clearer idea why his claim was rejected.

In sum, Krivan discloses most aspects of Tzipori's claim 26. Krivan lacks "human or humanized antibodies," monoclonal antibodies, and an explicit statement that the antibodies it discloses can "neutraliz[e]" SLT-II. These gaps are filled in by Queen, Perera, and Williams. Queen discloses a method of humanizing antibodies from

[14] Appellant Arthur Donohue-Rolfe is, as noted above, one of the inventors listed on the '958 application.

another species. Perera discloses a method of making monoclonal antibodies. And to the extent a reference is necessary that specifically discloses neutralizing SLT-II with antibodies, both Williams and Perera describe their antibodies as "neutralizing." All elements of claim 26 are present in the prior art, and the examiner and the Board reasonably concluded that someone with an advanced degree and relevant work experience would combine the teachings of Krivan, Queen, Perera, and Williams. The Board properly found that the invention embodied by claim 26 would have been prima facie obvious.

g. Secondary Indicia of Nonobviousness

Tzipori argues that even if claim 26 is prima facie obvious, his evidence of a long-felt but unmet need for a treatment for hemolytic uremic syndrome overcomes this prima facie case. However, as the Board pointed out, Krivan claims a method of treating "SLT toxemia in a human." Krivan at 20:16.

Additionally, Tzipori argues that his claims are allowable because he discovered that antibodies to the alpha subunit of SLT-II are more effective than antibodies against the beta subunit, and he submitted letters containing praise for his gnotobiotic pig model. As discussed above, these arguments of Tzipori's are divorced from the actual claims of the '958 application.

Tzipori also argues that the record contained additional evidence that the Board should have considered. However, Tzipori does not show us when (if ever) he directed the Board's attention to this material. He instead argues that the record was small enough that the Board should have considered his additional evidence. We, of course,

reject this argument; one of the purposes of Tzipori's brief to the Board is to identify any evidence he believes supports the allowability of his claims.

As we have previously noted, "[g]ood science and useful contributions do not necessarily result in patentability." PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1364 (Fed. Cir. 2007). The Board correctly determined that Tzipori did not rebutt the prima facie showing of obviousness. The rejection of claim 26 is upheld.

2. Claims 27 through 29

The Board selected claim 28 as representative of claims 27 through 29. Claim 28 depends from claim 26 and adds the limitation that "the antibodies are produced by recombinant DNA technology." In his brief, Tzipori admits that Queen teaches a method of making recombinant antibodies.[15] See, e.g., Queen at 4:11-29 (stating that humanized antibodies "of the present invention may be produced readily by a variety of recombinant DNA techniques").

The Board properly determined that the invention of claim 28 would have been obvious, and therefore the Board's rejection of claims 27 through 29 was proper.

3. Claims 30 and 33

The Board selected claim 30 as representative of claims 30 and 33. Claim 30 depends from claim 26 and adds the limitation that "the antibodies bind to the alpha subunit of the Shiga like toxin II." Perera discloses "monoclonal antibodies" which

[15] Additionally, at oral argument, the Director pointed out that Tzipori's specification contains the following passage that indicates making antibodies using recombinant DNA technology was known to those of ordinary skill in the art: "[M]onoclonal antibodies which specifically bind ST, SLT-I or SLT-II can be produced by recombinant DNA methodology. . . . One means of doing this is through the production of a phage display library and the selection of clones with the appropriate specificity (Monoclonal Antibodies from Combinatorial Libraries, Cold Spring Harbor Course, (1993))."

"immunoprecipitated the isolated A subunit of SLT-II." Perera at 2127. Because Perera was part of the combination of references used to find claim 26 obvious, the Board did not err in adding this disclosure from Perera to the combined disclosure used to find claim 26 obvious.

The Board therefore properly rejected claims 30 and 33 as obvious.

4. Claim 31

Claim 31 depends from claim 26 and adds the limitation that "the antibodies are effective to prevent neurological signs of hemolytic uremic syndrome or lesions, wherein the neurological signs or lesions are selected from the group consisting of bloody diarrhea, acute renal failure, cerebral hemorrhaging, bacterial shedding into feces, bacterial lesions, paddling, head-pressing, ataxia, convulsions, and wasting." The Board affirmed the examiner's determination that the invention of claim 31 would have been obvious because Krivan recites that one goal of his invention is "treating, preventing, or ameliorating illness or infection in a human or animal host caused by SLTs" and one of "[t]he primary diseases to be targeted" is "bloody diarrhea." Krivan at 10:30-32, 44-47. As Krivan is the primary reference for rejecting claim 26, this additional section of Krivan may be reasonably combined with the collection of references used to find that the invention embodied by claim 26 would have been obvious.

The Board therefore properly determined that the invention of claim 31 would have been obvious in light of the prior art.

5. Claims 32 and 34 through 36

The Board selected claim 32 as representative of claims 32 and 34 through 36. Claim 32 adds the limitation that "the antibodies are effective to prolong survival." The Board affirmed the examiner's finding that a portion of Krivan already used against claim 26 necessarily also disclosed prolonging survival. Krivan states, "A therapeutically or effective amount of the purified IgG or the purified antibodies of the invention are administered to the human or animal host." Krivan at 6:37-43. The difference between the prior art of "[a] therapeutically or prophylactically effective amount" and the claimed amount "effective to prolong survival" is so slight as to be necessarily obvious. See 35 U.S.C. § 103(a).

The Board thus properly rejected claims 32 and 34 through 36 as obvious.

III. CONCLUSION

The Board properly considered only representative claims of Tzipori's patent application, and the Board committed no reversible error in determining these representative claims all would have been obvious in light of the prior art. The decision of the Board of Patent Appeals and Interferences is therefore affirmed.