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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ECKHARD R. PODACK and LEI FANG¹

Appeal 2014-006893
Application 13/596,458
Technology Center 1600

Before DONALD E. ADAMS, LORA M. GREEN, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134(a) involves claims to methods of treating autoimmune diseases and preventing allograft rejections. The Examiner rejected the claims for lack of enablement and obviousness-type double patenting.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The Specification discloses that “Death Receptor 3 (DR3) . . . is a member of the TNF-receptor family The cognate ligand for DR3 has recently been identified as TL1A.” Spec. ¶ 8 (citations omitted). According

¹ Appellants state that the “real party in interest is the UNIVERSITY OF MIAMI, the assignee of the application on appeal.” Br. 3.

to the Specification, “[d]espite a significant amount of preliminary research, the physiological function of DR3 remains poorly characterized.” *Id.* ¶ 10.

Appellants’ invention, in one embodiment, “is based on the further characterization of the physiological function of DR3 on peripheral T cells and the discovery that DR3 plays an important role in the development of inflammatory lung disease (asthma).” *Id.* ¶ 41. In particular, “[t]he data obtained indicated that DR3 is upregulated very early during T cell activation by alternative splicing and that it contributes to the regulation of Th1/Th2 polarization of CD4 cells.” *Id.*

The Specification discloses that, “[b]ecause DR3 initiates dominant Th2 polarization, increasing DR3 activity will be beneficial in autoimmune syndromes dominated by Th1 activity. These include multiple sclerosis, rheumatoid arthritis and others.” *Id.* ¶ 96.

The Specification explains further:

Polarizing a T cell response toward a Th1 or Th2 pathway by modulating DR3 activity should be useful for treating a number of diseases. For example, suppressing Th2 responses with DR3 blockers should be helpful for treating asthma and for the immunotherapy of tumors. Enhancing Th2 responses with DR3 agonists, on the other hand, should be beneficial for treating Th1-dominated autoimmunity and for reducing the risk of transplant rejection.

Id. ¶ 101.

The Specification contains *in vivo* working examples, which include Example 2 (generation of a transgenic mouse model for lung inflammation (*id.* ¶¶ 133– 141)), Example 5 (use of mice to evaluate the role of CD30, another member of TNF receptor family, in lung inflammation (*id.* ¶¶ 147– 149)), Example 6 (use of mice to investigate the signaling requirements for

IL-13 production by CD30 (*id.* ¶¶ 150–151)), Examples 8 and 9 (use of mice to show that anti-CD30 antibodies interfere with resolution of EAE (Experimental Autoimmune Encephalomyelitis), an experimentally induced disorder in mice similar to multiple sclerosis in man (*id.* ¶¶ 153–154); *see also* Siegel² ¶ 391 (EAE is Experimental Autoimmune Encephalomyelitis)), Example 10 (transgenic mice used to show that administering “one or more agents that block both CD30 and DR3 signaling is expected to allow synergistic inhibition of IL-13 signaling, and such a combination can be used to treat inflammatory lung disease, including asthma” (Spec. ¶ 159)), and Example 11 (mice used to show expression of DR3 and its ligand TL1A in different types of immune cells in lymph nodes (*id.* ¶ 160–164)).

Claims 3 and 4 are the appealed claims and read as follows (Br. 9):

Claim 3: A method of treating a subject having a Th1-dominated autoimmune disease, the method comprising the step of administering to the subject an amount of an agonistic anti-DR3 monoclonal antibody sufficient to increase a Th2 immune response in the subject and treat the Th1-dominated autoimmune disease.

Claim 4: A method of preventing allograft rejection a subject that has or will receive an allograft, the method comprising the step of administering to the subject an amount of an agonistic anti-DR3 monoclonal antibody sufficient to reduce the chance that the subject will reject the allograft.

The following rejections are before us for review:

(1) Claims 3 and 4, under 35 U.S.C. § 112, first paragraph, for lack of enablement (Final Action 2–5; Ans. 2–5),

² Richard M. Siegel et al., US 2012/0263718 A1 (published Oct. 18, 2012).

(2) Claims 3 and 4, provisionally, under the judicially created doctrine of nonstatutory obviousness-type double patenting over claims 26–31 (now claims 1–8, 13, and 14) of copending application serial number 13/388,722 (Final Action 7; Ans. 6); and

(3) Claim 4, under the judicially created doctrine of nonstatutory obviousness-type double patenting over claims 1 and 3–5 of copending application serial number 13/457,583 (Final Action 7; Ans. 6). Because application serial number 13/457,583 issued as U.S. Patent No. 9,017,679 B2 on April 28, 2015, this is no longer a provisional rejection.

Appellants do not address the double patenting rejections in their Appeal Brief. Accordingly, we summarily affirm them. *See* MPEP § 1205.02 (“If a ground of rejection stated by the examiner is not addressed in the appellant’s brief, appellant has waived any challenge to that ground of rejection and the Board may summarily sustain it, unless the examiner subsequently withdrew the rejection in the examiner’s answer.”).

ENABLEMENT

The Examiner’s Position

In rejecting claims 3 and 4 for lack of enablement, the Examiner initially summarized the disclosures in the Specification, including the assertions, noted above, that administering DR3 agonists were expected by the inventors to be beneficial for treating autoimmune syndromes dominated by Th1 activity, such as multiple sclerosis and rheumatoid arthritis, and also for avoiding transplant rejection. Final Action 2–3.

The Examiner, however, cited a number of references to show that TL1A, the ligand of the DR3 receptor, actually exacerbates inflammation

and autoimmune disorders, thus directly contradicting the assertions in the Specification. *Id.* at 3–4 (citing Bull,³ Jin,⁴ Rafia,⁵ Zhang,⁶ and Pappu⁷).

As further evidence contradicting the Specification, Examiner cited two patent application publications claiming treatment of autoimmune disorders by blocking DR3 and TL1A interaction. *Id.* at 4 (citing Siegel and Burkly⁸).

As still further evidence contradicting the assertions in the Specification that autoimmune disorders and transplant rejection should be treatable by administering DR3 agonists, the Examiner cited Migone⁹ as evidence that “interaction of TL1A with DR3 promotes T cell expansion during an immune response,” and that “TL1A potently enhances acute graft-versus-host rejections.” *Id.* at 4.

³ Melanie Jane Bull et al., *The Death Receptor 3-TNF-like protein 1A pathway drives adverse bone pathology in inflammatory arthritis*, 205 *J. Exp. Med.* 2457–2464 (2008).

⁴ S. Jin et al., *TL1A/TNFSF15 directly induces proinflammatory cytokines, including TNF α , from CD3+CD161+ T cells to exacerbate gut inflammation*, *Mucosal Immunol.*, Dec. 19, 2012 (advance online publication).

⁵ Rafia S. Al-Lamki et al., *TL1A Both Promotes and Protects from Renal Inflammation and Injury*, 19 *J. Am. Soc. Nephrol.* 953–960 (2008).

⁶ Jun Zhang et al., *Role of TL1A in the Pathogenesis of Rheumatoid Arthritis*, 183 *J. Immunol.* 5350–5357 (2009).

⁷ Bhanu P. Pappu, *TL1A-DR3 interaction regulates Th17 cell function and Th17-mediated autoimmune disease*, 205 *J. Exp. Med.* 1049–1062 (2008).

⁸ Linda Burkly et al., US 2009/0317388 A1 (published Dec. 24, 2009).

⁹ Thi-Sau Migone et al., *TL1A Is a TNF-like Ligand for DR3 and TR6/DcR3 and Functions as a T Cell Costimulator*, 16 *Immunity* 479–492 (2002).

As to the assertions in the Specification that autoimmune disorders should be treatable by administering DR3 agonists, the Examiner stated that the “influence of a scientific theory should depend on its empirical and demonstrable aspects and not its underlying logic,” but found that “such underlying logic, empirical and demonstrable aspects of the claimed method of modulating DR3 activity in a subject using an agonistic anti-DR3 antibody are lacked in the instant specification.” Final Action 5.

In particular, the Examiner found that the Specification does not provide empirical data to show the efficacy of the agonistic anti-DR3 monoclonal antibody on the modulation of DR3 activity in a subject. It is not clear that the skilled artisan could predict the efficacy of the agonistic anti-DR3 antibody on the modulation of DR3 activity in a subject encompassed by the claims.

Id. The Examiner found also that a reasonable correlation did not exist between the animal tests described in the Specification and the scope of the claimed subject matter. *Id.*; *see also* Ans. 13 (arguing “[t]he lack of any working examples”).

Accordingly, the Examiner concluded, “[i]n view o[f] the quantity of experimentation necessary[,] the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art[,] and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.” Final Action 5.

Analysis

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):
[T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .

After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

Appellants' arguments do not persuade us that a preponderance of the evidence fails to support the Examiner's prima facie case of lack of enablement as to claims 3 and 4.

“The scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.” *National Recovery Technols. Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999).

However, “[t]ossing out the mere germ of an idea does not constitute enabling disclosure.” *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Instead, “[w]hile every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.” *Id.*

The well-known factors to be considered in evaluating whether experimentation would be undue include:

(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

In the instant case, claim 3 recites a method of treating a subject having a Th1 dominated autoimmune disease by administering to the subject

an agonistic anti DR3 monoclonal antibody in an amount sufficient to increase a Th2 immune response in the subject and treat the Th1 dominated autoimmune disease. Br. 9. As disclosed in the Specification, Th1 dominated autoimmune diseases include multiple sclerosis and rheumatoid arthritis. Spec. ¶ 96.

Claim 4 recites a method of preventing allograft rejection in a subject that has or will receive an allograft by administering an agonistic anti-DR3 monoclonal antibody in an amount sufficient to reduce the chance that the subject will reject the allograft. Br. 9.

Appellants do not dispute, nor do we discern any error in, the Examiner's finding (*see, e.g.*, Ans. 13) that the Specification fails to disclose any working examples encompassed by either claim 3 or claim 4.

Appellants do not dispute, nor do we discern any error in, the Examiner's finding (*see, e.g.*, Final Action 5; Ans. 8, 15–16) that the animal tests described in the Specification lack a reasonable correlation to the therapeutic processes recited in claims 3 and 4. As noted above, the sole *in vivo* examples relating to the rejected claims are Examples 8 and 9, which involve EAE, a mouse disorder similar to the multiple sclerosis encompassed by claim 3. Spec. ¶¶ 153–154. Those examples, however, do not involve or examine the role of DR3 in treating that disorder, but instead investigate the effects of inhibiting CD30, a different protein. *See id.*

Appellants do not dispute, nor do we discern any error in, the Examiner's finding (*see, e.g.*, Final Action 5) that the art involved in the therapeutic processes recited in claims 3 and 4 is unpredictable. To that end, we note the following unrebutted finding by the Examiner:

The lack of any working examples is exacerbated because the invention is in a highly unpredictable art-Th1-dominated [sic] autoimmune disease treatment and allograft rejection prevention- and while the level of skill of in the art may be high, the state of the prior art is that it is in fact unknown and untested what are the underlying physiologic bases of the therapeutic effects of agonistic anti-DR3 antibody in the treatment of Th1-dominated autoimmune disease and prevention of allograft rejection.

Ans. 13.

In addition to not rebutting or disputing the Examiner's findings, noted above, about the Specification's deficiencies and the high unpredictability in the art, Appellants also do not dispute, nor have they provided an evidentiary basis to conclude, that the references cited by the Examiner, because of their publication dates, fail to represent the state of the art at the time the instant application was effectively filed. Rather, Appellants contend only that a more thorough examination of the evidence demonstrates that the references cited by the Examiner are not "scientifically inconsistent," nor do they "contradict the subject matter of claims 3 and 4." Br. 7–8 (citing Paquet,¹⁰ Ortmann,¹¹ and Nikolic¹²).

We do not find Appellants' arguments persuasive. Appellants contend that the antigen-induced arthritis described in the Bull reference

¹⁰ Joseph Paquet et al., *Cytokines profiling by multiplex analysis in experimental arthritis: which pathophysiological relevance for articular versus systemic mediators?*, 14 *Arthritis Research and Therapy* R60 (2012).

¹¹ R.A. Ortmann and E.M. Shevach, *Susceptibility to collagen-induced arthritis: cytokine-mediated regulation*, 98 *J. Clin. Immunol.* 109–118 (2001) (abstract only).

¹² Boris Nikolic et al., *Th1 and Th2 mediate acute graft-versus-host disease, each with distinct end-organ targets*, 105 *J. Clin. Invest.* 1289–98 (2000).

cited by the Examiner is not a Th1-dominated disorder, based on Paquet's disclosure that "induction of this condition results in a decrease of IFN-gamma and an increase of IL-4 and IL-13 (which is more like a Th2-dominated disease)." Br. 7. Appellants do not, however, identify any specific persuasive evidence of record, in Paquet or elsewhere, supporting their assertion that a disorder exhibiting a decrease in IFN-gamma and an increase of IL-4 and IL-13 is more like a Th2-dominated disease than a Th1-dominated disease.

As noted above, moreover, rheumatoid arthritis is one of the disorders identified in the Specification as being treatable according to the methods of Appellants' claim 3. Spec. ¶ 96. As the Examiner found, Bull expressly states that its experimental disorder is an animal model for rheumatoid arthritis, and that disorder is treated by antagonizing DR3/TL1 activity, directly contrary to the treatment recited in claim 3, and the assertions in the Specification noted above:

[A]bsence of DR3 confers resistance to the development of adverse bone pathology in experimental antigen-induced arthritis (AIA). . . . In contrast, TNF-like protein 1A (TL1A), the ligand for DR3, exacerbated disease in a dose- and DR3-dependent fashion. . . . Treatment with antagonistic anti-TL1A mAb protected animals in a systemic model of RA [rheumatoid arthritis] disease collagen-induced arthritis.

Bull 2457 (abstract).

We acknowledge, but are not persuaded by, Appellants' assertions that

Jin does not present any data from animals showing what a DR3 agonist might do in a Th1-dominated disease (but rather only describes in vitro experiments and expression of TL1A in gut tissue). Rafia does not describe anything about Th1 or Th2-

dominated autoimmune disease, and only speculates about DR3/TL1A in other diseases.

Br. 7.

While it might be true that Jin does not provide animal data to support its findings, Appellants' Specification suffers from the same deficiency in supporting the hypothesis underlying the treatment methods recited in claims 3 and 4, as discussed above. In any event, as the Examiner found, both Jin and Rafia disclose that DR3/TL1A interaction promote inflammation, a result antithetical to treatments for autoimmune disorders or allograft rejection. *See* Jin 1, abstract (“We found that TL1A induces proinflammatory cytokines”); *see also* Rafia 953, abstract (“[Our] data suggest that TL1A may contribute to renal inflammation and injury through DR3-mediated activation of NF- κ B and caspase-3, respectively”).

We acknowledge, but are not persuaded by, Appellants' contention that Zhang's collagen-induced arthritis model “is not strictly a Th1-dominated disease,” based on the Ortmann abstract's assertion that Th2 cytokines may be important in Zhang's model. Br. 7; *see also* Ortmann, abstract.

As the Examiner found, Zhang uses its experimentally induced arthritis as a mouse model for rheumatoid arthritis (*see* Zhang 5350 (abstract)), which is one of the disorders identified in the Specification as being treatable according to the methods of Appellants' claim 3. Spec. ¶ 96. If anything, therefore, Ortmann undercuts the assertion in Appellants' Specification that rheumatoid arthritis is a disorder treatable according to the method of claim 3. Moreover, we note that, in addition to the data

suggesting that DR3/TL1A aggravates the mouse arthritis model, Zhang also examined human tissues and made a similar finding:

We further showed that human rheumatoid arthritis (RA) synovial fluids had elevated TL1A titers, and human chondrocytes and synovial fibroblasts were capable of secreting TL1A upon TNF- α or IL-1 β stimulation. Taken together, these data suggest that TL1A secretion in lymphoid organs might contribute to RA initiation by promoting autoantibody production, and TL1A secretion stimulated by inflammatory cytokines in RA joints might be a part of a vicious circle that aggravates RA pathogenesis.

Zhang 5350 (abstract).

We find Appellants' assertions regarding the Pappu reference (Br. 7) similarly unpersuasive. Pappu used the animal model disorder EAE to show that the absence of TL1A reduces the severity of autoimmune disorders, thus contradicting the assertions in Appellants' Specification. Pappu 1049 (abstract)). EAE is described in Appellants' Specification as a model for multiple sclerosis (Spec. ¶ 153), one of the autoimmune disorders treatable according to the method of Appellants' claim 3 (*see id.* ¶ 96).

We find Appellants' assertions regarding the Migone reference (Br. 7–8) similarly unpersuasive. We acknowledge Nikolic's disclosure that both Th1 and Th2 cells contribute to graft versus host disease (GVHD). Nikolic 1289. As the Examiner found, however, Migone discloses that TL1A, the ligand for DR3, promotes inflammatory responses, which Appellants do not dispute is antithetical to claim 3's treatments of autoimmune disorders, and also, "in vivo, it potently enhances acute graft-versus-host reactions" (Migone 479), which contradicts the premise underlying claim 4's method of treating allograft rejection by administering a DR3 agonist. Appellants

assert that Migone’s model does not involve allograft rejection. Br. 7. Appellants, however, do not explain persuasively how Migone’s showing, that TL1A (the ligand for DR3) potentiates the immune reaction to an allograft, fails to undercut the hypothesis underlying the process recited in Appellants’ claim 4, that administering a DR3 agonist would ameliorate allograft rejection.

As to claim 4, in rebuttal to Rafia’s suggestion that TL1A-mediated DR3 signaling is involved in allograft rejection (*see, e.g.*, Rafia 953–954), Appellants assert that, according to the Specification, “[i]f Th2 polarization is induced before the start of the allograft rejection process (where DR3 expression is induced in renal tubular epithelial cells and vascular endothelial cells), then apoptosis of the cells in the allograft will not be induced by DR3 signaling.” Br. 8. Appellants do not, however, direct us to specific persuasive evidence supporting this assertion. To the contrary, this assertion is a reiteration of the hypothesis stated in the Specification, which, as discussed above, lacks substantiating evidence in the form of working examples or relevant experiments in animal models.

Lastly, we note that Appellants do not address or rebut either the Siegel or Burkly reference, both of which disclose treating autoimmune disorders by antagonizing DR3, directly contrary to the premise underlying the treatment in Appellants’ claim 3. *See* Siegel, abstract (“treating inflammatory autoimmune diseases in a subject comprising blocking the interaction between DR3 and TL1A”); *see also* Burkly ¶ 2 (“administering, to a subject who has multiple sclerosis, an agent that blocks TL1A signaling, e.g., an agent that blocks TL1A interaction with DR3”).

In sum, based on the totality of the evidence, including the absence of working examples and the absence of relevant experiments using a clearly correlating animal model in the Specification, as well as the unpredictability in the art and the references cited by the Examiner contradicting the theoretical premises underlying the treatment methods recited in claims 3 and 4, Appellants do not persuade us that a preponderance of the evidence fails to support the Examiner's conclusion that claims 3 and 4 lack an enabling disclosure in the Specification.

SUMMARY

For the reasons discussed, we affirm the Examiner's rejection of claims 3 and 4 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

We also affirm the provisional rejection of claims 3 and 4 for obviousness-type double patenting over claims 26–31 (now claims 1–8, 13, and 14) of copending application serial number 13/388,722.

We also affirm the rejection of claim 4 for obviousness-type double patenting over claims 1 and 3–5 of application serial number 13/457,583, which issued as U.S. Patent No. 9,017,679 B2 on April 28, 2015.

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