UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MICHAEL WINKLER and HORST RUECKOLDT

Appeal 2008-3466
Application 10/094,966
Technology Center 1600

Decided: July 30, 2008

Before ERIC GRIMES, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 8-12 and 17-21. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to methods of preventing rejection of porcine xenotransplants in primates and humans. Claims 8 and 17 are representative of the claims on appeal, and read as follows:

8. A method for preventing hyperacute rejection of porcine xenotransplants in mammals comprising administration of immunosuppressant therapy and a preparation comprising a therapeutically effective amount of a C1 esterase inhibitor (C1-INH) to a primate or human recipient organism.

17. A method for delaying acute rejection of porcine xenotransplants in mammals comprising administration of immunosuppressant therapy and a preparation comprising a therapeutically effective amount of a C1 esterase inhibitor (C1-INH) to a primate or human recipient organism.

The Examiner relies on the following references:

Elizabeth A. Davis et al., *Inhibition of Complement, Evoked Antibody, and Cellular Response Prevents Rejection of Pig-to-Primate Cardiac Xenografts*, 62 TRANSPLANTATION 1018-1023 (1996).

Brigitte Heckl-Ostreicher et al., *Protection of Porcine Endothelial Cells From Complement-Mediated Cytotoxicity by the Human Complement Regulators CD59, C1 Inhibitor, and Soluble Complement Receptor Type 1*, 62 TRANSPLANTATION 1693-1696 (1996).

M. Loss et al., *Acute vascular rejection is associated with systemic complement activation in a pig-to-primate kidney xenograft model,* 2000 XENOTRANSPLANTATION 186-196 (2000).

Arnt E. Fiane et al., *Cl-inhibitor attenuates hyperacute rejection and inhibits complement, leukocyte and platelet activation in an ex vivo pig-to-human perfusion model*, 42 IMMUNOPHARMACOLOGY 231-243 (1999).

The Examiner contends that claims 8-12 and 17-21, all of the claims on Appeal, are obvious over the combination of Davis, Heckl-Ostreicher, and Loss.

Appellants contend that sCR1 and C1-INH are not functionally equivalent, thus there would have been no reasonable expectation of success in arriving at the claimed invention.

Thus, the issue on Appeal is: Has the Examiner set forth a prima facie case of obviousness that all of the claims on Appeal are obvious over the combination of Davis, Heckl-Ostreicher and Loss?

FINDINGS OF FACT

The Scope and Content of the Prior Art

Davis

FF1. Davis is relied upon by the Examiner for teaching "the administration of sCR1 [soluble complement receptor type 1] in combination with cyclosporine, cyclophosphamide and steroids for the prevention of [hyperacute rejection] HAR and [acute vascular rejection] AVR (called AAR by Davis et al.) in porcine to cynomolgus monkey xenotransplants." (Ans. 5; Davis Abstract.)

FF2. Davis teaches that sCR1 was administered prior to transplant and daily following the transplant (Ans. 5; Davis p. 1019, second column).

FF3. Davis additionally teaches that sCR1 is a known complement inhibitor (Ans. 5; Davis Abstract).

FF4. The monkeys treated in Davis "showed minimal evidence of rejection at the time of their deaths due to systemic infections." (Ans. 5; Davis Abstract.)

Heckl-Ostreicher

FF5. Heckl-Ostreicher is relied upon by the Examiner for teaching "that the complement inhibitors sCR1 and C1-INH protect an *in vitro* porcine to primate xenotransplantation model system from complement-mediated cytotoxicity." (Ans. 5; Heckl-Ostreicher Abstract.)

FF6. Heckl-Ostreicher, according to the Examiner, while disclosing that "sCR1 had a higher potency [on a molar basis] than C1-INH, they clearly suggest that C1-INH will likely have two advantages *in vivo*"; those advantages being that "C1-INH not only inhibits the classical pathway of the complement system but also is a regulator of the coagulation system, which is known to also contribute to hyperacute rejection and as an inhibitor of only the classical pathway of complement [,] use of C1-INH would leave the alternative pathway available to protect the immunosuppressed graft recipient against infections." (Ans. 5-6; Heckl-Ostreicher 1694.)

FF7. According to Heckl-Ostreicher, "[s]elective inhibition of C1 may be sufficient in species combinations such as pig/human, where complement is mainly activated via the classical complement pathway." (Heckl-Ostreicher 1694.)

FF8. Heckl-Ostreicher teaches further that C1-INH, which is a major plasma inhibitor of the complement and contact systems, "has long been used for the treatment of the hereditary angioedema, has recently been introduced as substitution therapy in patients with vascular leak syndrome, severe sepsis, and myocardial ischemia/reperfusion injury." (Heckl-Ostreicher 1694.)

Loss

FF9. Loss is cited by the Examiner for teaching "porcine to cynomolgus monkey xenotransplants using pig kidney transgenic for human regulators of complement activation." (Ans. 6, Loss Abstract.)

FF10. Loss treated the monkeys with immunosuppressive therapy comprised of cyclosporine, cyclophosphamide, and steroids (Ans. 6; Loss Abstract).

FF11. Loss is also cited by the Examiner for teaching that "this regimen[ ] led to a near complete abrogation of HAR and extended survival compared to previous xenotransplants but that most of the xenografts were still lost due to AVR despite the heavy immunosuppression." (Ans. 6; Loss Abstract.)

FF12. Loss suggests that the treatment regimen may be modified to include the administration of soluble regulators of complement activation such as sCR1 or C1-INH (Ans. 6; Loss 195).

Fiane[1]

FF13. Fiane is cited by the Examiner for teaching that C1-INH may have advantages in inhibiting complement in xenotransplantation (Ans. 8, Fiane Abstract).

FF14. Pig kidneys were perfused with human blood to which C1-INH or a control had been added, and the survival rate of kidneys perfused with the blood to which C1-INH had been added was significantly longer when compared to the control (Fiane, Abstract).

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[1] Although not specifically relied upon by the Examiner in rejecting the claims, Fiane is cited by the Specification (Spec. 14 (reference 22)), as well as by both the Examiner (Ans. 8) and Appellants (App. Br. 17-18).

FF15. Fiane teaches that:

> Compared with other strategies to inhibit complement in the fluid-phase, C1-INH has certain advantages. First, it is a physiological complement regulator which has been used for decades to treat patients with C1-INH deficiency. Although prepared from blood donors, the risk of disease transmission is low and immunisation is probably not involved. Second, the classical pathway is inhibited from the very beginning by C1-INH in contrast to agents that block C3 activation and the alternative pathway. Pig-to-human HAR is mediated through the classical pathway whereas the alternative pathway probably is of little importance (Baldwin et al., 1995). C1q promotes cell adhesion and activation, and C1q receptors are expressed on many immunocompetent and parenchymal cells involved in graft rejection, including platelets and neutrophils. These C1q effects in the HAR reaction may be dampened by using C1-INH in contrast to C3 inhibition. Classical pathway activation products from C2 and C4 may contribute to the inflammatory reaction (Baldwin et al., 1995, Cholin et al., 1989). Furthermore, an intact alternative pathway may be beneficial to avoid infections. Third, the effect of C1-INH is not limited to complement but also involves inhibition of the coagulation and contact systems, of which at least the former participates in the pathogenesis of HAR (Davis, 1988, Sundsmo and Fair, 1983). Finally, we suggest a major advantage with C1-INH to be the inhibitory effect on leukocyte and platelet activation that we have demonstrated in the present study.

(Fiane 241.)

The Level of Ordinary Skill in the Art

FF16. We find that one of ordinary skill in the art would have a very high level of skill, such as a Ph.D. or M.D. performing research in the transplant field.

The Differences between the Claimed Invention and the Prior Art

FF17. Davis teaches a method of preventing complement evoked pig-to-primate cardiac xenografts through the administration of sCR1 and standard immunosuppressive agents (Davis Abstract).

FF18. Davis fails to teach the use of the complement inhibitor C1-INH.

FF19. Heckl-Ostreicher determined that C1-INH protected porcine endothelial cells, a pig-to-human in vitro model relevant to hyperacute xenograft rejection, from complement mediated cytotoxicity (Heckl-Ostreicher Abstract).

FF20. Heckl-Ostreicher, Loss, and Fiane all suggest the use of C1-INH to prevent xenograft rejection, and both Heckl-Ostreicher and Fiane teach the advantages of using C1-INH.

FF21. The only difference between the instant disclosure supporting the claimed invention and the prior art is that the prior art never actually tested the use of C1-INH in an *in vivo* model.

ANALYSIS

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). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and

creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

The Examiner concludes that:

> Therefore, as Davis et al. have demonstrated that xenotransplants treated with both immunosuppressives and a soluble regulator of complement activation overcame HAR and showed minimal evidence of AVR, and as both Heckl-Ostreicher et al. and Loss et al. explicitly suggest that C1-INH would make a suitable soluble regulator of complement activation and Heckl-Ostreicher in fact teach that C1-INH likely would be a better choice *in vivo*, it would have been obvious to one of ordinary skill in the art to replace the sCR1 used by Davis et al. with C1-INH. Based on the disclosure of Heckl-Ostreicher et al., one of skill in the art would have used doses of C1-INH similar to or up to 15 fold greater than those used for treatment of myocardial ischemia (i.e. 15mg/kg body weight). Furthermore, as in the art the porcine to cynomolgus monkey xenotransplants system is the accepted model system for pig to human xenotransplants, it would have been further obvious to use a human as the recipient.

(Ans. 6-7.)

We conclude that the Examiner has set forth a prima facie case of obviousness. We thus turn to Appellants' arguments and evidence in rebuttal.

Appellants group claims 8-12 together (App. Br. 12). We focus our analysis on independent claim 8, and claims 9-12 stand or fall with that claim.

Appellants' primary argument is that sCR1 and C1-INH are not functionally equivalent (App. Br. 12-15). Appellants cite the Declaration of Dr. Gerhard Dickneite ("Dickneite Declaration," dated April 5, 2006) as evidence demonstrating the differences between the two proteins (App. Br.

13). Thus, Appellants argue, "[w]hen these differences are considered in the in the context of the very complicated myriad of complement and clotting reactions that take place in a living system, the skilled artisan would not have a reasonable expectation of success in substituting C1-INH into the *in vivo* model of *Davis* based solely on information about how C1-INH may work *in vitro*." (*Id.* at 14.)

We do not find Appellants' argument convincing. The differences between sCR-1 and C1-INH would have been recognized by the authors of the Heckl-Ostreicher, Loss, and Fiane references, and yet each reference suggested the use of C1-INH in preventing xenotransplant rejection. In fact, it is because of those differences that both Heckl-Ostreicher and Fiane suggest that C1-INH may have advantages over sCR-1 *in vivo*, such as the fact that C1-INH only inhibits the classical complement pathway, thus leaving an alternative complement pathway available to protect the immunosuppressed graft recipient against infection.

As to the Dickneite Declaration, it reiterates the functional differences between sCR1 and C1-INH argued in the Appeal Brief (Dickneite Declaration ¶¶ 10-12), and renders the opinion that "[b]ased upon the total teachings of the[ ] references and my knowledge of the art of complement regulators, I believe that the skilled artisan would not consider C1-inh and sCR1 to be functionally equivalent compounds *in vivo*." (*Id.* at ¶ 9.) Thus, the Declaration addresses the ultimate legal issue of obviousness, and thus is not entitled to much weight. *In re Reuter*, 670 F.2d 1015, 1021 (CCPA 1981).

Appellants argue further that none of Davis, Heckl-Ostreicher, and Loss disclose experiments wherein C1-INH was used *in vivo* (App. Br. 14).

According to Appellants, "although *in vitro* experiments may be useful as an initial study of a drug's effectiveness, they do not necessarily predict efficacy *in vivo*." (*Id.*) Thus, given the differences between sCR1 and C1-INH, Appellants reiterate that there is no expectation of success (*id.*)

Appellants argue further that the combination of references relied upon by the Examiner, at best, rises to the level of an invitation to experiment (*id.* at 15). According to Appellants, the statements in Heckl-Ostreicher relied upon by the Examiner of why C1-INH may be a better choice than sCR1 are "purely theoretical and neutral at best." (*Id.* at 16.) Moreover, Appellants assert, those statements "do not cure the lack of a reasonable expectation of success." (*Id.*)

As to Fiane, Appellants argue that the statement in Fiane that C1-INH has certain advantages "should be taken in context of the study in which porcine kidneys were removed and perfused with human blood *in vitro*." (App. Br. 17-18.) According to Appellants, Fiane's model of using an organ and testing outside the body "is not all that different" from Heckl-Ostreicher's which uses cells from a pig, thus Fiane's statement "that C1-INH has 'certain advantages' cannot be applied to *in vivo* use." (*Id.* at 18.)

Again, Appellants' arguments are not convincing. As noted above, Heckl-Ostreicher (FF5), Loss (FF12), and Fiane (FF13) all suggest using C1-INH to prevent rejection in xenotransplantation, and Heckl-Ostreicher (FF6) and Fiane (FF15) both teach that certain advantages may be obtained using C1-INH in *in vivo* methods.

We acknowledge that the *in vitro* experiments are not always predictive of *in vivo* results. But as noted by Heckl-Ostreicher (FF6), the prior art recognizes reasons why one would want to inhibit both complement

and contact pathways. Moreover, Heckl-Ostreicher (FF5) presents success of using C1-INH in an *in vitro* model and Fiane (FF14) presents success with an *ex vivo* model. Thus, as set forth above, the only difference between the prior art and the disclosure supporting the instant claims is that Appellants have performed the next logical experiment—performing an *in vivo* experiment in which porcine kidneys were transplanted into cynomolgus monkeys (Spec. 5-6). We conclude, however, that the fact that the prior art did not perform that experiment does not render the claimed method unobvious, as based on the *in vitro* experiments performed in the xenotransplantation model of Heckl-Ostreicher (FF5), as well as the *ex vivo* experiments of Fiane (FF14), coupled with the fact that C1-INH has been used *in vivo* for other uses, provides the ordinary artisan a reasonable expectation of success of obtaining favorable results, such as those reported in Appellants' Specification, using a primate *in vivo* model.

Finally, both Appellants' (App. Br. 14-15; Reply Br. 9-11) and the Examiner's arguments (Ans. 12-13) regarding dosage have been considered, but as claim 8 does not require any particular dosage, we need not consider those arguments here. Moreover, we consider dosage to be a result-effective variable, which would be well within the level of the skill of the ordinary artisan to determine. *See In re Boesch*, 617 F.2d 272, 276 (CCPA 1980) (determining the optimum values of result effective variables is ordinarily within the skill of the art).

Appellants group claims 17-21 together (App. Br. 18). As Appellants essentially only reiterate their arguments as to claims 8-12 (*id.*), the rejection is affirmed as to claims 17-21 for the reasons set forth above.

CONCLUSIONS OF LAW

We conclude that the Examiner has set forth a prima facie case of obviousness as to claims 8-12 and 17-21 that has not been adequately rebutted by Appellants.

TIME LIMITS

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

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