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EXAMINER

JIANG, DONG

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CHARLES DINARELLO,
BENJAMIN POMERANTZ, LEONID REZNIKOV,
ALDEN HARKEN, and YOLANDE CHVATCHKO¹

Appeal 2015-006793
Application 10/470,303
Technology Center 1600

Before JEFFREY N. FREDMAN, JOHN G. NEW, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

¹ Appellants state the real parties-in-interest are Merck Serono SA and Yeda Research and Development Company Ltd. App. Br. 3.

SUMMARY

Appellants file this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 40, 45–47, 53, 56, and 57² as unpatentable under the 35 U.S.C. § 103(a) as being obvious over the combination of Torigoe et al. (WO 00/12555, March 9, 2000)³ (“Torigoe”) and B.S. Cain et al., *Therapeutic Strategies to Reduce TNF-alpha Mediated Cardiac Contractile Depression following Ischemia and Reperfusion*. 31 J. MOL. CELL CARDIOL. 931–947 (1999) (“Cain”).

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

We AFFIRM.

NATURE OF THE CLAIMED INVENTION

Appellants' invention is directed to the use of an inhibitor of IL-18 in the preparation of a medicament for treatment and/or prevention of a heart disease, in particular ischemic heart disease. Combinations of an IL-18 inhibitor and/or a TNF- α antagonist are also considered for the treatment and/or prevention of a heart disease. Abstract.

REPRESENTATIVE CLAIM

Appellants argue all of the claims together. *See* App. Br. 9.

Independent claim 53 is representative of the claims on appeal and recites:

53. A method for improving ventricular function and contractile dysfunction of the heart in ischemic cardiomyopathy comprising, selection of a host with ischemic cardiomyopathy,

² Claims 1–39, 41–44, 48–52, 54, and 55 are canceled. App. Br. 13.

³ We rely upon the English language equivalent for translation, US 2005/0191303 A1, published Sept. 1, 2005.

and then administering to the host affected with ischemic cardiomyopathy IL-18 binding protein isoform a or a functional derivative of IL-18 binding protein isoform a comprising at least one polyethylene glycol moiety attached to a functional group occurring as a side chain on an amino acid residue of IL-18 binding protein isoform a and a pharmaceutically effective amount of a Tumor Necrosis Factor (TNF) antagonist thereby improving ventricular function and contractile dysfunction of the heart in ischemic cardiomyopathy.

App. Br. 13.

ISSUES AND ANALYSIS

We agree with, and adopt, the Examiner's findings and conclusion that the appealed claims are obvious. We address the arguments raised by Appellants on appeal below.

Issue

Appellants argue that the Examiner erred by failing to properly weigh the evidence of record that Appellants contend demonstrates a person of ordinary skill in the art would not have been motivated to combine the cited references to arrive at Appellants' claimed invention. App. Br. 9.

FINDINGS OF FACT

F.1 Sakao teaches:

LPS triggers the production of several inflammatory mediators including TNF- α , IL-1, IL-6, IL-12, IFN- γ and NO. Among these mediators, TNF- α has been shown to be one of the factors most responsible for the pathogenesis of septic shock. It is now hypothesized that TNF- α , which is produced and released in the first 2 h of endotoxin shock, induces several mediators such as IL-1 β , IFN- γ and NO, which leads to serious systemic disorders.

Sakao 476–77 (internal citations omitted).

- F. 2 Sakao teaches: “[A] study using anti-IL-18 antibody has revealed that IL-18 is also involved in the induction of liver injury. *P. acnes*-primed IL-18KO mice were resistant to LPS-induced liver injury, confirming an important role for IL-18 in the induction of liver injury.” *Id.* at 477 (internal citations omitted).
- F.3 Sakao teaches: “*P. acnes*-primed IL-18KO mice showed greater susceptibility to LPS-induced septic shock than did wild-type mice These observations, together with the results from studies using TNF-R p55- and TNF- α -deficient mice, support that TNF- α plays a central role in the pathogenesis of septic shock.” *Id.* at 478.
- F4. Sakao concludes: “the present study demonstrates that IL-18 suppresses TNF- α production from monocytes/macrophages in response to LPS during *P. acnes* priming, and that IL-18 plays an important role in the pathogenesis of sepsis.” *Id.* at 479 (emphasis added).
- F.5 Seta I teaches: “This study shows that circulating concentrations of IL-18 increase in patients with acute MI [myocardial infarction]. We hypothesize that higher concentrations of IL-18 may be a new marker of cardiac damage in the development of acute MI.” Seta I. 668.

- F.6 Seta II teaches: “Plasma IL-18 concentration was significantly higher in patients with CHF [congestive heart failure] than in 15 healthy volunteers.” Seta II Abstr.
- F. 7 Torigoe teaches IL-18BP, and further teaches that IL-18BP binding to IL-18 can suppress the activity of IL-18, which can be efficacious in the treatment of various diseases, including ischemia and ischemic cardiac myopathy. *See* Torigoe ¶¶ 9, 28, Abstr..
- F. 8 Cain teaches that TNF- α directly depresses human myocardial contractility. Cain 931.
- F.9 Cain teaches TNF- α alone is sufficient to cause dilated cardiomyopathy and failure. Cain 932.
- F.10 Cain teaches: “strategies to reduce or neutralize post-ischemic TNF- α production should improve post-ischemic myocardial function.” *Id.* at 934.
- F. 11 Cain teaches that neutralizing TNF- α activity with either TNF binding protein or anti-TNF antibodies increased post-ischemic function in rat myocardium and also improved post-ischemic left ventricular developed pressure in the isolated rat heart. *Id.* at 937.

ANALYSIS

Appellants argue that Torigoe is limited to teaching IL-18 binding protein (“IL-18BP”), whereas Cain teaches “TNF-[α] neutralization with

either TNF binding protein (“TNFBP”) or anti-TNF[- α] antibody increased post-ischemic function in rat myocardium, or improved post-ischemic left ventricular developed pressure in the isolated rat heart....” App. Br. 9 (quoting Non-Final Act., July 13, 2012). Appellants assert that a person of ordinary skill in the art would not have been motivated to combine the separate teachings of Torigoe and Cain to arrive at Appellants’ claimed combination of IL-18BP and a TNF antagonist because “one of skill in the art would have been aware that the art, at the time the invention was made, taught that a combination of IL-18 antagonists and TNF antagonists would not be a beneficial combination.” *Id.*

Appellants adduce Y. Sakao et al., *IL-18-Deficient Mice are Resistant to Endotoxin-Induced Liver Injury but Highly Susceptible to Endotoxin Shock*, 11(3) INT. IMMUNOL. 471–480 (1999) (“Sakao”) in support of their argument. App. Br. 10. According to Appellants, Sakao teaches, *inter alia*, inhibition of IL-18 leads to an increase in TNF- α levels. *Id.* Appellants contend, a person of ordinary skill in the art would not have combined IL-18 inhibitors with TNF- α inhibitors because Sakao teaches that TNF- α inhibition would increase IL-18 levels. *Id.* Consequently, Appellants argue, “[t]he sum effect of a combination of a IL-18 inhibitor and TNF- α in view of Sakao would have been expected to be at most zero”; with the TNF- α antagonist cancelling out the effect of IL-18BP. *Id.*

In response to Appellants’ arguments in this respect, the Examiner points to Y. Seta et al., *Interleukin 18 in Acute Myocardial Infarction*, 84 HEART 668 (2000) (“Seta I”) and Y. Seta et al., *Interleukin-18 in Patients with Congestive Heart Failure: Induction of Atrial Natriuretic Peptide Gene Expression*, 108(1–2) RES. COMMUN. MOL. PATHOL. PHARMACOL. 87–95

(2000) (“Seta II”) to rebut the teachings of Sakao. App. Br. 10. Appellants contend that Seta I and Seta II teach only the correlation of IL-18 levels with heart disease. *Id.* at 11. Appellants assert neither Seta I nor Seta II provides a teaching or suggestion concerning TNF- α , or of the combination of IL-18BP and TNF- α antagonists. *Id.* Appellants do not dispute the Examiner’s finding that IL-18 inhibition and TNF- α inhibition were both known in the art for the treatment of cardiovascular diseases. *Id.* Rather, Appellants argue that, regardless of what was known about the use of each compound individually, Sakao teaches that the two compounds would be expected to counteract each other, and therefore there was a direct teaching away from the combination of IL-18BP and a TNF- α antagonist for any purposes. *Id.*

Furthermore, Appellants contend, the Examiner’s finding that Sakao teaches a disease model other than ischemic cardiomyopathy does not discredit the relevant teaching of Sakao. App. Br. 11. Regardless of what disease model Sakao used, Appellants argue, Sakao teaches that inhibitors of IL-18 increased the expression of TNF- α . *Id.* Therefore, Appellants assert, a TNF- α antagonist would be expected to produce an effect that counteracts at least part of the effect of IL-18 inhibition. *Id.*

The Examiner responds that the animal model taught by Sakao is lipopolysaccharide (“LPS”)-induced liver injury and endotoxin shock in *Propionibacterium acnes*-primed IL-18-deficient (IL-18 knockout) mice, which is not an experimental model recognized in the art as equivalent to ischemic cardiomyopathy, as recited in the claims. Ans. 5. The Examiner also finds the animals employed in Sakao are IL-18 knockout (IL-18KO) mice, which do not exist in nature; therefore, the Examiner finds, such an animal model does not resemble any real world clinical condition, let alone

ischemic cardiomyopathy. *Id.* The Examiner finds that the model taught by Sakao is not even remotely representative of, or relevant to, ischemic cardiomyopathy, Appellants' reliance on Sakao is not probative of the obviousness of the claims, and does not arise to the level of a "teaching away." *Id.*

In contrast, the Examiner finds, Seta I teaches changes in the release of IL-18 in human patients with (ischemic) coronary artery disease by examining the correlation between IL-18 concentrations and the serum activities of myocardial enzymes, estimating myocardial necrosis or atrial natriuretic peptide (ANP). Ans. 6 (citing Seta I 668). The Examiner finds Seta I teaches plasma IL-18 concentrations were significantly higher in patients with acute myocardial infarction ("MI") than in controls, which may induce apoptosis in myocytes, leading to persistent myocardial damage in acute MI. *Id.* The Examiner also finds Seta I teaches that increased secretion of IL-18 occurs in patients with acute MI and correlates with the severity of myocardial damage. *Id.*

The Examiner finds Seta II teaches studies of human patients with coronary artery disease ("CAD"), including patients with angina pectoris and congestive heart failure ("CHF"). Ans. 6 (citing Seta II 88). The Examiner finds Seta II teaches circulating IL-18 was significantly higher in patients with CHF than the control group, whereas patients with angina pectoris had no significant increase of plasma IL-18. *Id.* (citing Seta II 91). The Examiner finds further that Seta II concludes that increased secretion of IL-18 in patients with CHF correlates with the severity of heart failure, and indicates the study results suggest that anti-IL-18 therapy may reduce cardiac hypertrophy in patients with CHF. *Id.* (citing Seta II 93).

The Examiner finds it would therefore have been obvious to a person of ordinary skill in the art that that IL-18 plays a pathological role in the development of ischemic heart disease including ischemic cardiomyopathy (ischemic heart failure). Ans. 6–7. Consequently, the Examiner concludes, a person of ordinary skill would have had a reasonable expectation that the combination of agents antagonizing IL-18 and TNF- α would be successful in treating ischemic cardiomyopathy, as taught by the combined cited prior art references. *Id.* at 7.

We are not persuaded by Appellants' arguments. Appellants do not dispute the Examiner's findings that the combination of Torigoe and Cain teaches all of the limitations of the claims on appeal. Rather, Appellants argue that another prior art reference teaches away from Appellants' invention such that a person of ordinary skill in the art would not be motivated to combine the reference teachings relied upon by the Examiner. We disagree with Appellants that Sakao teaches away.

Specifically, Sakao teaches:

LPS triggers the production of several inflammatory mediators including TNF- α , IL-1, IL-6, IL-12, IFN- γ and NO. Among these mediators, TNF- α has been shown to be one of the factors most responsible for the pathogenesis of septic shock. It is now hypothesized that TNF- α , which is produced and released in the first 2 h of endotoxin shock, induces several mediators such as IL-1 β , IFN- γ and NO, which leads to serious systemic disorders.

F.1 (internal citations omitted). Sakao also teaches: “[A] study using anti-IL-18 antibody has revealed that IL-18 is also involved in the induction of liver injury. *P acnes*-primed IL-18KO mice were resistant to LPS-induced liver injury, confirming an important role for IL-18 in the induction of liver

injury.” F. 2 (internal citations omitted). And Sakao teaches: “*P. acnes*-primed IL-18KO mice showed greater susceptibility to LPS-induced septic shock than did wild-type mice These observations, together with the results from studies using TNF-R p55- and TNF- α -deficient mice, support that TNF- α plays a central role in the pathogenesis of septic shock.” F.3. Finally, Sakao concludes: “the present study demonstrates that IL-18 suppresses TNF- α production from monocytes/macrophages *in response to LPS during P. acnes priming*, and that IL-18 plays an important role in the pathogenesis of sepsis.” F. 4 (emphasis added).

In light of Sakao’s disclosure, we find that Sakao teaches the absence of IL-18 promotes TNF- α production in response to bacterially-primed, LPS-induced liver injury. Sakao, however, is not directed to a chemically-induced myocardial injury, as are Appellants’ claims.

Both Seta I and Seta II teach that IL-18 levels are elevated in patients suffering ischemic cardiac injury. F. 5, 6. Torigoe teaches IL-18BP, and further teaches that IL-18BP binding to IL-18 can suppress the activity of IL-18, which can be efficacious in the treatment of various diseases, including ischemia and ischemic cardiac myopathy. F. 7.

Cain teaches that TNF- α directly depresses human myocardial contractility and that that TNF- α alone is sufficient to cause dilated cardiomyopathy and failure. F. 8, 9. Cain also teaches: “strategies to reduce or neutralize post-ischemic TNF- α production should improve post-ischemic myocardial function.” F. 10. Cain further teaches that neutralizing TNF- α activity with either TNF binding protein or anti-TNF antibodies increased post-ischemic function in rat myocardium and also improved post-ischemic left ventricular developed pressure in the isolated rat heart. F. 11.

We are not persuaded that the teachings of Sakao are sufficient to overcome these combined cited prior art references relied upon by the Examiner. Torigoe and Cain together teach that suppression of both IL-18 and TNF- α levels is useful in reducing ischemia-induced myocardial injury. Seta I and II teach that IL-18 levels are increased following ischemic insult to the heart, whereas Cain teaches that TNF- α levels are similarly increased following myocardial infarction. Cain Abstr. We find that a person of ordinary skill in the art would realize that the combined teachings of the references indicate that, following ischemic injury to the myocardium, levels of both IL-18 and TNF- α are increased.

Sakao teaches that IL-18 suppresses TNF- α production from monocytes/macrophages in response to LPS during *P. acnes* priming, however, this interaction is in the context of a bacterially-primed, endotoxin-induced liver injury. Appellants adduce no evidence suggesting that the same interaction occurs within the context of ischemic injury to the tissues of the heart. Consequently, we are not persuaded that, given the difference in the injury models between Sakao and the Examiner's cited references, a person of ordinary skill would necessarily have concluded that the teachings of Sakao are of sufficient weight to overcome the teachings of the cited references and, therefore, further conclude that there would be no reasonable expectation of success in combining the references.

More importantly, a teaching away requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Appellants adduce no teaching or suggestion by Sakao that IL-18BP and a TNF- α inhibitor should not be combined when treating ischemia-induced myocardial injury. In the

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absence of any such direct teaching, or persuasive evidence that Sakao is a relevant model system, we conclude that Sakao cannot be said to teach away from Appellants' claimed invention, and we therefore affirm the Examiner's rejection of the claims.

DECISION

The Examiner's rejection of claims 40, 45–47, 53, 56, and 57 as unpatentable under 35 U.S.C. § 103(a) is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED