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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JALIL BENYACOUB, BLAISE CORTHESY, STEPHANIE BLUM-SPERISEN, and LAURENT FAVRE [1]

Appeal 2019-003679
Application 15/468,961
Technology Center 1600

Before JEFFREY N. FREDMAN, DEBORAH KATZ, and JOHN G. NEW, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] We use the term "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as Nestec S.A. App. Br. 2.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 1–17 as unpatentable under 35 U.S.C. § 112 (pre-AIA), first paragraph, for failing to comply with the enablement requirement.

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

We AFFIRM.

NATURE OF THE CLAIMED INVENTION

Appellant's invention is directed to a method of treating non-viral infections by administering a combination of probiotics and secretory IgA ("SIgA"). Spec. ¶¶ 2, 38.

REPRESENTATIVE CLAIM

Claim 1 is representative of the claims on appeal and recites:

> 1. A method for treating non-viral infections, the method comprising the step of:
>
> administering to a subject in need thereof a therap[e]utically-effective amount of a composition comprising SIgA and probiotic microorganisms,
>
> wherein the SIgA and the probiotic microorganisms are present in the form of a complex with each other, and
>
> the SIgA and the probiotic micro-organisms are present in the composition in a stoichiometric ratio of at least 100:1.

App. Br. 10.

ISSUES AND ANALYSIS

We agree with, and expressly adopt, the Examiner's findings, reasoning, and conclusion that the claims fail to comply with the enablement requirement. We address the arguments raised by Appellant below.

Issue

Appellant argues that the examples of the Specification provide enablement for the presently claimed method. App. Br. 6.

Analysis

The Examiner determines that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the inventions commensurate in scope with these claims." Ans. 3. In making the determination, the Examiner addresses the factors set forth in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). *Id.* at 4. The Examiner finds the scope of the claims encompasses "treating any and all non-viral infections such as bacterial, parasites, fungi, prion and protozoan infections, by administering to any kind[] of subject, … a therapeutically effective amount of a composition comprising SIgA and probiotic microorganisms." *Id.* at 5. The Examiner finds that the "art is highly unpredictable." *Id.* The Examiner finds that the "instant specification fails to provide any experiments that show that a method for treating any and all non-viral infections for individuals at risk for infection by various species of non-viral microorganisms which would be effective in protecting a human or other animal against any type of non-viral infection." *Id.*

In considering the *in vitro* tests disclosed by the Specification, the Examiner finds Appellant has "failed to demonstrate a reasonable correlation to the treatment of any non-viral infection." Ans. 6. The Examiner finds that "[t]here is no evidence that the examples within the specification are predictive of a method of treating any non-viral infection. The *in vitro* experiments do not correlate to treatment of any specific non-viral disease." *Id.* at 9.

With respect to the Declaration of Jalil Benyacoub, Ph.D., filed June 4, 2018 (the "Benyacoub Decl."), the Examiner finds that the "Declarant does not correlate the *in vitro* experiments to any specific condition." Ans. 16. The Examiner finds "Declarant has not provided [] extrapolative evidence to correlate the *in vitro* experiments to any specific non-viral infection." *Id.* More specifically, the Examiner finds evidence that the probiotic-SIgA complex: 1) induces activation of transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells ("NF-κB"), 2) induces production of thymic stromal lymphopoeitin ("TSLP"), and 3) increases expression of polymeric Ig receptor ("pIgR"), is not correlated to the treatment of any non-viral infection. *See id.* at 16–20.

Appellant argues that "the examples in the specification provide experimental evidence that SIgA and probiotics are responsible for increasing the immune response involved in the treatment and reduction of all kind of non-viral infections." Reply Br. 2. Appellant argues that the Benyacoub Declaration and accompanying references disclose "that the experimental examples in the specification 'correlate' with the presently claimed invention and therefore, constitute 'working examples' that provide enablement for the claimed invention." *Id.* at 3 (emphasis omitted).

The Benyacoub Declaration discloses that the probiotic-SIgA complex induces activation of transcription factor NF-κB. Benyacoub Decl. 2, citing Spec. Example 3; Mathias A., et al., *Potentiation of Polarized Intestinal Caco-2 Cell Responsiveness to Probiotics Complexed with Secretory IgA*, 285 J. BIOL. CHEM. 33906–33913 (2010) ("Mathias 2010"). "Broad activation [of NF-κB] will predispose the immune system to be more reactive and efficient to antigenic challenges which is key to support defences [sic] against multiple infections of various []etiologies." Reply Br. 3. The Benyacoub Declaration discloses that the probiotic-SIgA complex promotes the production of TSLP. *Id.*, citing Mathias 2010. "This cytokine is instrumental in activation of dentritic cells as well as B cells, two major immune components for the defences [sic] against pathogens irrespective of pathogen[] origin, could it be bacteria or parasites or helminths. *Id.* The Benyacoub Declaration discloses that the probiotic-SIgA complex increases expression of pIgR. *Id.* at 2–3, citing Spec. Fig. 7. "pIgR is essential for the secretion of the SIgA produced by the host and is thus a key factor[] in protection of the host against infections, including of non-viral []etiology." *Id.* The Benyacoub Declaration discloses the probiotic-SIgA complex can lead to enhanced production of mucosal IgA in a host. *Id.* at 3, citing Mathias A., et al., *Role of secretory IgA in the mucosal sensing of commensal bacteria*, 5 GUT MICROBES 685–695 (2014) ("Mathias 2014"). "The overall role of SIgA in protecting the host against pathogens is well documented and this includes bacteria, parasites or helminths." *Id.* Appellant argues that "the skilled artisan, given the level of knowledge and skill in the art, would be able to correlate the experimental examples in the application with the claimed methods of treating non-viral infections and

therefore, be able to practice the claimed invention without undue experimentation." Reply Br. 4.

We are not persuaded by Appellant's arguments. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Wands*, 858 F.2d at 737. Appellant does not dispute the Examiner's findings that the claims have a very broad scope, i.e., treating any non-viral infection.[2] The references cited by Appellant confirm the Examiner's

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[2] We note that the extreme breadth of "non-viral infection" as disclosed in the Specification includes a very large and diverse set of diseases:

> Typical bacterial infectious diseases that can be treated or prevented by the present invention include salmonellosis, shigellosis, typhoid fever, bacterial meningitis, anthrax, botulism, brucellosis, campylobacteriosis, cat scratch disease, cholera, diphtheria, epidemic typhus, gonorrhea, impetigo, legionellosis, leprosy (Hansen's Disease), leptospirosis, listeriosis, lyme disease, melioidosis, rheumatic fever, MRSA infection, nocardiosis, pertussis (whooping cough), plague, pneumococcal pneumonia, psittacosis, Q fever, Rocky Mountain Spotted Fever (RMSF), scarlet fever, syphilis, tetanus, trachoma, tuberculosis, tularaemia, typhus, and/or urinary tract infections.
>
> Typical parasitic infectious diseases that can be treated or prevented by the present invention include african trypanosomiasis, amebiasis, ascariasis, babesiosis, Chagas disease, clonorchiasis, cryptosporidiosis, cysticercosis, diphyllobothriasis, dracunculiasis, echinococcosis, enterobiasis, fascioliasis, fasciolopsiasis, filariasis, free-living amebic infection, giardiasis, gnathostomiasis, hymenolepiasis, isosporiasis, kala-azar, leishmaniasis, malaria, metagonimiasis, myias1s, onchocerciasis, pediculosis, pmworm infection,

finding of a high level of unpredictability in the art. *See In re Goodman*, 11 F.3d 1046, 1051 (Fed. Cir. 2005) ("the references cited by [Appellant] to show enablement support the Board's position that great uncertainties encumbered [the technology]"). For example, Mathias 2010 discloses that "[t]he role of probiotic and commensal bacteria in the physiology of the gastrointestinal tract is incompletely understood, … [and] the mechanisms underlying the beneficial effects of probiotics … are still in need of investigation." Mathias 2010, 33912. Mathias 2014 discloses that "[t]he importance of commensal bacteria in the maintenance of the integrity of intestinal epithelial cell (IEC) barrier and the control of the underlying immune mechanisms ensuring homeostasis is a fundamental process, whose multiple and complex features are not yet fully understood." Mathias 2014, 689.

Given the broad reach of the claims in an unpredictable field, Appellant relies on the *in vitro* examples of the Specification as enabling the claims. "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a

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> scabies, schistosomiasis, taeniasis, toxocariasis, toxoplasmosis, trichinellosis, trichinosis, trichuriasis, trichomoniasis, and/or trypanosomiasis.
>
> Typical fungal infectious diseases that can be treated or prevented by the present invention include aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, and/or tinea pedis.

(Spec. ¶¶ 47–49).

disclosed or claimed method invention. *Edwards Lifesciences AG v. CoreValve, Inc.*, 699 F.3d 1305, 1310 (Fed. Cir. 2012). Only a reasonable correlation is necessary "where the disclosure of pharmacological activity is reasonable based on the probative evidence." *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985). As discussed in detail below, we conclude that the *in vitro* examples and references cited in the Benyacoub Declaration are not reasonably correlated to the pharmacological activity of treating any non-viral infection.

Example 1 discloses that SIgA improves probiotic binding capacity to Caco-2 epithelial cells. Spec. ¶¶ 78–84. Example 2 discloses incubating epithelial cells with probiotic-SIgA complex increases transepithelial electrical resistance ("TER"). Spec. ¶¶ 85–89. Appellant does not explain any correlation between either of Examples 1 and 2 and treating non-viral infections.

Example 3 discloses incubating epithelial cells with probiotic-SIgA complex "reduced NF-κB activation" as compared to exposure to the probiotic (*Lactobacillus rhamnosus* ("LPR")) alone, or to pathogenic bacteria. Spec. ¶¶ 90–95. According to Mathias 2010, "[t]his indicates that exposure of epithelial cells to certain probiotic microorganisms such as LPR … maintains a low, if not basal, degree of NF-κB activation that may be instrumental for the maintenance of homeostasis." Mathias 2010, 33912. Moreover, "induction of NF-κB after exposure to ... SIgA-probiotic complexes did not lead to the production by Caco-2 cells of chemokines involved in the recruitment of pro-inflammatory cells." *Id.* We do not find this *in vitro* example to be probative evidence of treating a non-viral infection.

Example 4 discloses pre-treating epithelial cells with the probiotic-SIgA complex "reduced the infection of polarized Caco-2 cell monolayer by *S. flexneri*." Spec. ¶¶ 96–100. This example arguably discloses the pharmacological activity of one probiotic complex with one bacterial infection. However, Appellant has not established a correlation between this specific example and the breadth of the claims, in particular, establishing a "therapeutically-effective amount" for a subject for treating any non-viral infection. *Cf. Cross*, 753 F3d. at 1052 ("This is not a case such as *In re Gardner*, 427 F.2d 786, 166 USPQ 138 (1970), where the CCPA held that the applicant's disclosure was nonenabling because inventive skill and undue experimentation would be required to discover appropriate dosages for humans, i.e., a therapeutic use.")

Example 5 discloses incubating epithelial cells with the probiotic-SIgA complex increased pIgR synthesis. Spec. ¶¶ 101–107. According to Mathias 2010, "[t]hese results indicate that the interaction between a probiotic-SIgA complex and epithelial Caco-2 cells prompts these latter to synthesize more pIgR involved in mucosal defense." Mathias 2010, 33911. We do not find this *in vitro* example to be probative evidence of treating a non-viral infection.

We further consider examples of the probiotic-SIgA complex increasing production of TSLP and mucosal IgA as disclosed in the Benyacoub Declaration. There is no teaching in the Mathias references for a correlation between these mechanisms and treating a non-viral infection. Like the other interactions between the probiotic-SIgA complex and the immune system of the gastrointestinal tract, "[t]hese data provide partial clues as to the still puzzling issue of how SIgA contributes to the complex

mechanisms of actively regulating mucosal immune homeostasis, in particular discrimination between noxious and resident microorganisms." Mathias 2014, 691.

Because Appellant has not shown a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, we conclude that Appellant's disclosure is nonenabling for the full scope of the claimed invention, as inventive skill and undue experimentation would be required to discover appropriate methods for treating non-viral infection. *See Cross*, 753 F.2d at 1052. "Thus, at the end of the day, the specification, even read in the light of the knowledge of those skilled in the art, does no more than state a hypothesis and propose testing to determine the accuracy of that hypothesis. That is not sufficient." *In re '318 Patent Infringement Litig*., 583 F.3d 1317, 1327 (Fed. Cir. 2009). Accordingly, we sustain the Examiner's rejection.

CONCLUSION

The rejection of claims 1–17 as unpatentable under 35 U.S.C. §112, first paragraph, 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).

AFFIRMED

Claims Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
1–17	112, first paragraph	Enablement	1–17	
Overall Outcome			1–17	