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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JAMES J. COLLINS, MICHAEL KOERIS, TIMOTHY KUAN-TA LU, TANGUY MY CHAU, GREGORY STEPHANOPOULOS, and CHRISTOPHER YOON

Appeal 2017-008640
Application 13/224,776
Technology Center 1600

Before JEFFREY N. FREDMAN, TAWEN CHANG, and DAVID D. COTTA, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134(a) involving claims to an engineered bacteriophage. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as Trustees of Boston University and Massachusetts Institute of Technology (*see* App. Br. 3).

[2] We have considered and refer to the Specification of Sept. 2, 2011 ("Spec."); Final Action of Jan. 28, 2016 ("Final Act."); Appeal Brief of Jan. 26, 2017 ("App. Br."); Examiner's Answer of Mar. 27, 2017 ("Ans."); and Reply Brief of May 26, 2017 ("Reply Br.").

Statement of the Case

Background

"Bacterial infections are responsible for significant morbidity and mortality in clinical settings" (Spec. ¶ 6). "Bacteriophages (often known simply as 'phages') are viruses that grow within bacteria" (*id.* ¶ 14).

> Using bacteriophage to kill bacteria has been in practice since the early 20th century . . . Bacteriophage can be chosen to lyse and kill bacteria or can be modified to express lethal genes to cause cell death. However, bacteriophage which are directly lethal to their bacterial hosts can also produce phage-resistant bacteria in short amounts of time.

(*id.* ¶ 11). The Specification teaches the "inventors have demonstrated, using an engineered bacteriophage expressing antimicrobial polypeptides (e.g. antimicrobial peptides or lytic enzymes), [that] they are able to delay the development of bacteriophage resistance and have achieved long-term suppression of phage resistance of bacteria by at least 40 hours or more" (*id.* ¶ 28).

The Claims

Claims 15–20, 24, and 26–36 are on appeal. Claim 15 is representative and reads as follows:

> 15. An engineered bacteriophage comprising an exogenous nucleic acid operatively linked to a promoter, wherein the nucleic acid encodes at least one antimicrobial polypeptide fused to an N-terminal secretory signal sequence, and wherein the antimicrobial polypeptide is expressed by and secreted from a bacterial host cell infected with the engineered bacteriophage by the N-terminal secretory signal sequence, and wherein the expression of the antimicrobial polypeptide can reduce the viability of a heterogeneous bacterial population not infected with the engineered bacteriophage.

The Issues

The Examiner rejected the claims on the following grounds:

Claim(s) Rejected	Basis	Examiner's Rejection
15, 16, 26–29, 31, 33–36	§ 103(a) over Schaak,[3] Takahara[4]	Ans. 3–4
17	§ 103(a) over Schaak, Takahara, Boman[5]	Ans. 4–5
18–20	§ 103(a) over Schaak, Takahara, Horgan,[6] CHAP[7]	Ans. 5–6
24	§ 103(a) over Schaak, Takahara, Westwater[8]	Ans. 6–7
30	§ 103(a) over Schaak, Takahara, Murphy[9]	Ans. 7–8
15, 16, 26–29, 32, 35, 36	§ 103(a) over Schaak, Sargent[10]	Ans. 8–9
17	§ 103(a) over Schaak, Sargent, Boman	Ans. 9–10
18–20	§ 103(a) over Schaak, Sargent, Horgan, CHAP	Ans. 10–11

[3] Schaak, US 6,759,229 B2, issued July 6, 2004.
[4] Takahara et al., *The ompA Signal Peptide Directed Secretion of Staphylococcal Nuclease A by Escherichia coli*, 260 J. Biol. Chem. 2670–4 (1985).
[5] Boman, EP 0 403 458 A1, published Dec. 19, 1990.
[6] Horgan et al., *Phage Lysin LysK Can Be Truncated to Its CHAP Domain and Retain Lytic Activity against Live Antibiotic-Resistant Staphylococci*, 75 Applied Environ. Microbiol. 872–4 (2009).
[7] CHAP, Genbank Accession No. YP_241096 (2007).
[8] Westwater et al., *Use of Genetically Engineered Phage To Deliver Antimicrobial Agents to Bacteria: an Alternative Therapy for Treatment of Bacterial Infections*, 47 Antimicrob. Agents Chemotherapy 1301–7 (2003).
[9] Murphy et al., US 2007/0207209 A1, published Sept. 6, 2007.
[10] Sargent et al., *Pathfinders and trailblazers: a prokaryotic targeting system for transport of folded proteins*, 254 FEMS Microbiol. Lett. 198–207 (2005).

Claim(s) Rejected	Basis	Examiner's Rejection
24	§ 103(a) over Schaak, Sargent, Westwater	Ans. 11–12
30	§ 103(a) over Schaak, Sargent, Murphy	Ans. 9–10

Because these rejections all rely upon Schaak and either Takahara or Sargent, the same issue relates to all the rejections, and we will consider these rejections together.

The Examiner finds Schaak teaches "an engineered bacteriophage comprising a nuclei[c] acid operatively linked to a promoter, wherein the nucleic acid encodes at least one antimicrobial polypeptide" (Ans. 3). The Examiner acknowledges Schaak does "not teach wherein the antimicrobial agent also encodes a signal sequence" (Ans. 4). The Examiner finds that either Takahara or Sargent teach signal peptides that can be fused to proteins for secretion outside the bacterial cell (Ans. 4, 9). The Examiner finds it obvious to "express a signal peptide capable of transporting a fused protein across the cytoplasmic membrane as Schaak et al. is interested in the production of a bacteriocide that could be taken up by surrounding bacteria" (Ans. 4, 9).

Appellant contends

> the motivation is the exact opposite of what the prior art teaches. If one attached a secretory signal sequence to the AMP of Schaak, Schaak teaches that the secreted AMP would have no anti-microbial effect on neighboring cells because that AMP is not toxic. So why would the skilled artisan want to attach a secretory sequence? The answer is, (s)he wouldn't. So there is no motivation to combine the references.

(App. Br. 6).

The issue with respect to these rejections is: Does the evidence of record support the Examiner's conclusion that the prior art renders the claims obvious?

Findings of Fact

1. Schaak teaches "toxin-phage bacteriocide (TPB) include bacteriophage that have been genetically engineered to encode a peptide toxin that can be expressed within the bacterial host cell. Within the bacterial host cell, the peptide toxin is active and functions to kill the bacterial host cell" (Schaak 3:23–27).

2. Schaak teaches "the nucleic acid molecule encoding the TPB peptide toxin includes a bacterial promoter and other sequences required to direct transcription and translation of TPB peptide toxin in the bacterial cell being targeted" (Schaak 4:29–32).

3. Schaak teaches "intracellular peptide toxins and peptide-like toxins that are toxic to a cell when inside the cell, but relatively non-toxic to the cell when outside the cell" (Schaak 3:16–18). Schaak further explains that the "peptide toxin, e.g., the TPB peptide toxin A, is toxic to cells, e.g., bacterial cells when it is present inside the cell, but not when it is outside of a cell" (Schaak 6:50–53).

4. Takahara teaches the "signal peptide is able to direct the secretion of fused staphylococcal nuclease A, and signal peptide processing occurs at the normal cleavage site" (Takahara 2670, abstract).

5. Sargent teaches the "twin-arginine (Tat) protein translocase is a highly unusual protein transport machine that is dedicated to the movement of folded proteins across the bacterial cytoplasmic membrane" (Sargent 198, abstract).

Principles of Law

A prima facie case for obviousness requires "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 418 (2007).

Analysis

While the Examiner did identify close prior art, the rejections fail to provide a persuasive reason to modify Schaak in view of either Takahara or Sargent to generate an antimicrobial peptide that is "secreted from a bacterial host cell" and that "can reduce the viability of a heterogeneous bacterial population not infected with the engineered bacteriophage," as required by claim 15. Claim 36, which is broader than claim 15, still requires a secretion signal sequence that will result in secretion of the antimicrobial peptide.

So while we agree with the Examiner that secretion signals were well known in the art (FF 4, 5) and that the ordinary artisan would have been able to generate a bacteriophage including such secretion signals for any protein of interest, Schaak specifically teaches that the expressed antimicrobial protein is only toxic to bacterial cells "when it is present inside the cell, but not when it is outside of a cell" (FF 3). Thus, the ordinary artisan would have had no reason to attach a secretion signal sequence to the antimicrobial protein of Schaak because such a signal would render the antimicrobial protein inactive against the bacteriophage infected bacteria: The antimicrobial peptide would exit the bacteria by secretion, where it would be nontoxic (FF 3), rather than killing the bacteria as desired by Schaak (FF 1).

In addition, even if Schaak's antimicrobial peptides were secreted for purification or other purposes unrelated to cell toxicity, Schaak has already

explained that they are not toxic to cells when outside the cell (FF 3). Therefore, Schaak's peptides would not function to "reduce the viability of a heterogeneous bacterial population not infected with the engineered bacteriophage," as also required by claim 15.

We appreciate the Examiner's argument that claim 15 "does not state that the surrounding cells cannot take up the antimicrobial polypeptide where it is toxic" (Ans. 14). However, the Examiner provides no evidence or persuasive reasoning that surrounding cells would inherently take up the toxic antimicrobial peptide or that the prior art provides a suggestion to further modify the toxic antimicrobial peptide with elements that would allow the peptide to enter uninfected cells.

We disagree with the Examiner's statement that "there is no limitation on how the antimicrobial peptide functions at all" (Ans. 14), because claim 15 does impose a specific limitation, that the secreted antimicrobial peptide functions to "reduce the viability of a heterogeneous bacterial population not infected with the engineered bacteriophage" (Claim 15). Bacteriophage that express secreted antimicrobial peptides that do not reduce the population of any uninfected bacteria do not fall within the scope of claim 15.

While the Examiner does not separately address claim 36, we note that no evidence was provided that suggests the use of an engineered bacteriophage as an expression system for antimicrobial proteins where secretion would allow easier purification or where there are other reasons to secrete the antimicrobial proteins.

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that the prior art renders the claims obvious.

CONCLUSION

In summary:

Claim(s) Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
15, 16, 26–29, 31, 33–36	§ 103(a)	Schaak, Takahara		15, 16, 26–29, 31, 33–36
17	§ 103(a)	Schaak, Takahara, Boman		17
18–20	§ 103(a)	Schaak, Takahara, Horgan, CHAP		18–20
24	§ 103(a)	Schaak, Takahara, Westwater		24
30	§ 103(a)	Schaak, Takahara, Murphy		30
15, 16, 26–29, 32, 35, 36	§ 103(a)	Schaak, Sargent		15, 16, 26–29, 32, 35, 36
17	§ 103(a)	Schaak, Sargent, Boman		17
18–20	§ 103(a)	Schaak, Sargent, Horgan, CHAP		18–20
24	§ 103(a)	Schaak, Sargent, Westwater		24
30	§ 103(a)	Schaak, Sargent, Murphy		30
Overall Outcome				15–20, 24, 26–36

REVERSED