Paper 18

Filed by: Trial Section Motions Panel
Box Interference

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

HERMAN A. DEBOER, REIN STRIJKER,
HERBERT L. HEYNEKER, GERARD PLATENBURG, SANG HE LEE,
FRANK PIEPER, and PAUL J.A. KRIMPENFORT,

Junior Party
(Patent Nos. 5,741,957, 6,013,857, and 6,140,552),

v.

KATHERINE GORDON, SUZANNE GROET, LOTHAR HENNIGHAUSEN, and
HEINER WESTPHAL,

Senior Party
(Application 08/246,259).

Patent Interference 105,004

Before: SCHAFER, TORCZON, and NAGUMO, Administrative Patent Judges.

NAGUMO, Administrative Patent Judge.

JUDGMENT
(Under 37 C.F.R. § 1.640)

NO INTERFERENCE-IN-FACT

1. The parties have submitted a joint motion for judgment that no interference-in-fact exists. (Paper No. 16, "JM".)

The count:

2. Count 1, the sole count, is:

a transgenic bovine according to claim 7 of Deboer 6,140,552 or a transgenic bovine according to claim 18 of Gordon, 08/246,259.

3. DeBoer claim 7 is:

A bovine whose mammary gland cells have a genome comprising in operable association:

a DNA sequence encoding a signal sequence functional in bovine mammary gland secretory cells;

a DNA sequence encoding a polypeptide of interest; and

a regulatory sequence that promotes expression of the DNA sequence encoding the polypeptide in the mammary gland;

wherein the bovine or a female descendant of the bovine is disposed to express the transgene in mammary secretory cells such that the polypeptide of interest is detectable in milk produced by the bovine or a female descendant of the bovine;

wherein the polypeptide is a heterologous polypeptide.

4. Gordon claim 18 is:

A non-human mammal whose genome comprises a DNA construct comprising a whey acidic protein promoter operably linked to a DNA sequence encoding a heterologous protein, wherein said construct further comprises a DNA sequence encoding a secretory peptide operatively linked to said DNA sequence encoding a heterologous protein, wherein said mammal is selected from the group consisting of mouse, sheep, pig, goat and cow, and wherein said heterologous protein is expressed in the milk of the mammal.

5. DeBoer's claim 7 relates exclusively to bovines, but it recites a general regulatory promoter sequence.

6. Gordon's claim 18 refers to a set of five mammals, including cow, which is a species of bovine, but it recites exclusively the whey acidic protein (WAP) promoter.

7. The parties argue that each of the claims of the three involved DeBoer patents (all of which correspond to the count) refers to a regulatory sequence that promotes expression, a mammary gland specific promoter, a mammary gland promoter or a regulatory sequence from a gene that is preferentially expressed in the mammary gland over the other tissues, or an alpha-s1 casein promoter. (JM at 2-3, ¶4.)

8. The parties argue further that each of Gordon's involved claims specifies a DNA construct in which the promoter is a whey acidic protein promoter (WAP) that is operably linked to a DNA sequence encoding a heterologous protein, and a DNA sequence encoding a signal peptide. (*Id.* at 3, ¶6.)

Technical background:

Testimony of Dr. Meade:

9. Dr. Harry M. Meade is Senior Vice President of Research at GTC, an assignee of the Gordon application. (Meade declaration, JE007 at 1, ¶2.)

10. Dr. Meade testified that he has worked and published extensively in the fields of molecular biology and transgenic

animal technology. (*Id.* at 1, ¶4.)

11. Dr. Meade testified that he is an inventor of U.S. Patent 4,873,316, which relates to the transgenic production of protein in milk using the casein promoter. (*Id.* at ¶3.)

12. Review of the face of U.S. Patent 4,873,316 shows that Dr. Meade is one of two inventors, that its title is "Isolation of Exogenous Recombinant Proteins from the Milk of Transgenic Mammals," and that it was filed June 23, 1987. (JE011 at 1.)

13. Dr. Meade states that whey acid protein is specific to rodents, and is not normally present in the milk of ruminants. (JE007 at 3, ¶7.)

14. According to Dr. Meade, there was no evidence in 1986 that the WAP promoter would function in bovines. (*Id.*)

15. Dr. Meade states that, in 1986, he thought it would have been more likely that a milk promoter from a ruminant would facilitate expression of heterologous proteins in ruminant milk. (*Id.* at ¶8.)

16. Dr. Meade further states that he is not aware of any example of successful expression of a heterologous protein in a transgenic animal prior to Gordon's priority date. (*Id.* at 3-4, ¶9.)

17. Moreover, Dr. Meade states that it was unknown whether a promoter from one species could effectively drive expression of a protein coding sequence from a second species in the mammary

gland of a third species. (*Id.*)

Testimony of Dr. Strijker

18. Dr. Rein Strijker, a co-inventor of the involved DeBoer patents, is also Chief Business Office at Pharming, the assignee. (Strijker declaration, JE005 at 1, ¶1.)

19. Dr. Strijker testified that he has extensive research experience and numerous publications in the art of eukaryotic gene expression and transgenic animals. (*Id.* at ¶2.)

20. In particular, Dr. Strijker states that he was especially familiar with the state of the art of eukaryotic promoters in 1986, as illustrated by the defense of his thesis, which contained a chapter on the topic, in March of that year. (*Id.* at 2, ¶6.)

21. Dr. Strijker testified that many eukaryotic genes have a highly conserved element called a TATA box about 30 base pairs (bp) upstream from the transcription start site. (*Id.*) Moreover, according to Dr. Strijker, it was well-known that mutations of the TATA regulatory sequence resulted in "severe reduction of transcription levels." (*Id.*)

22. Dr. Strijker testified further that eukaryotic genes often have a "CAAT box" upstream from the start site, and that mutations of this sequence also reduce transcriptional efficiency. (*Id.*) Dr. Strijker testified that still other regulatory sequences were known to exist in eukaryotic genes, but

that it was not known which sequences were required for promoter activity; nor was their location known. (*Id.* at 2-3.)

23. Dr. Strijker testified that he is unaware of anyone having successfully expressed a heterologous protein in the milk of a transgenic animal as of 1986. (*Id.* at 3, ¶7.)

24. Dr. Strijker also testified that as of 1986, "it had not been determined which, if any promoters, "were suitable for the task, and what if any other regulatory sequences might be required to achieve expression in milk." (*Id.*)

25. Dr. Strijker states that Campbell & Rosen (JE009), published in 1984, reports that the WAP promoter had a "very unusual TATA box," as well as a CAAT sequence. (JE005 at 4, ¶9.)

26. Review of Campbell and Rosen confirms Dr. Strijker's characterization: an upstream sequence, TTTAAAT, is described as "an unusual 'TATA box,' and another upstream sequence, CAAAGTCT, is described as "similar to the 'CAAT' box." Both sequences were located in the upstream portions of both mouse and rat WAP genes. (JE009 at 8694.)

27. Dr. Strijker states that he would have inferred from the unusual TATA box structure that the WAP promoter was "inherently extremely weak, and/or that the WAP promoter was regulated in a manner not yet known and probably requiring one or more additional sequences besides the TATA box and the CAAT region." (*Id.*) (JE005 at 4, ¶9.)

28. According to Dr. Strijker, nothing in Campbell & Rosen, or in the prior art available at the time, indicated whether the WAP gene had other regulatory promoter sequences, or where they were. (*Id.*)

29. Dr. Strijker states that the Rosen et al. reference (JE010), published March 30, 1986, reporting the failure to observe WAP gene expression in the majority of transfectants analyzed, is "entirely consistent with and reinforce" his conclusions based on the unusual TATA box reported for the WAP gene.

30. Review of Rosen confirms Dr. Strijker's characterization of that reference: Rosen reported that WAP gene expression was not observed in a majority of transfectants arising from the transfection of entire rat β-casein and WAP genes into mammary gland cells. (JE010 at 146.)

The parties' arguments

31. The parties urge that it would not have been obvious, given what was known about the WAP promoter, to use the WAP promoter to express a protein in bovine milk based on the broader genera or alternative species of promoter recited in the DeBoer claims. More specifically, they urge that nothing in the prior art would have motivated the selection of the WAP promoter, and that the state of the art actually taught away from using the WAP promoter.

32. Moreover, the parties urge that the early state of the art of making transgenic animals in 1986 would have further complicated matters because it would have been difficult to distinguish problems due to inherent structural features of the WAP promoter from general problems of expressing proteins in transgenic animals.

33. The parties conclude that expression using the WAP promoter, as recited in Gordon's claims, is patentably distinct from expression using the genera of promoters or the alternative casein promoter recited in the DeBoer claims. Accordingly, they urge that there is no interference-in-fact.

Discussion

Test and burden of proof

"No interference-in-fact" means there is no interfering subject matter, that one party's claims are no impediment to a patent for the other party's claims. The movant has the burden to prove that the other party claims a different invention from his own." *Case v. CPC Int'l, Inc.*, 730 F.2d 745, 750, 221 USPQ 196, 200 (Fed. Cir. 1984). In this context, "different invention" means "patentably distinct." *Aelony v. Arni*, 547 F.2d 566, 570, 192 USPQ 486, 490 (CCPA 1977) ("Sections 102, 103, and 135 of 35 U.S.C. clearly contemplate where different inventive entities are concerned that only one patent should issue for inventions which are either identical to or not patently distinct

from each other. . . . there is ample precedent from this court for framing the test of interference in fact in terms of whether two sets of claims are patentably distinct from each other.")

If either party in an interference shows that its involved claims would have been neither anticipated nor obvious over the other party's involved claims, then it has established that a precondition for an interference — that the two parties are claiming the same patentable invention — is not met. It is then evident that the interference was declared improvidently, and that it should be terminated.

On the merits of the joint motion

In the present case, two experts have testified as to the state of the art of expressing heterologous proteins in milk by transgenic techniques as of early 1986. We find that both Dr. Meade and Dr. Striker are qualified as experts in the field of transgenic expression of proteins in general, and as experts in the field of the transgenic expression of proteins in milk, in particular. Based on their patents and publications, we find that they were experts in and knowledgeable about the state of that art in 1986. We therefore accept and give significant weight to their statements that they were unaware of any example of successful expression of a heterologous protein in a transgenic animal prior to Gordon's priority date (JE007, Meade declaration at 3-4, ¶9), or, more specifically, unaware of anyone

having successfully expressing a heterologous protein in the milk of a transgenic animal as of 1986. (JE005, Strijker declaration at 3, ¶7.) We conclude that the technical development of the field of the inventions was at an early stage in 1986. Consistently, Dr. Meade states that it was unknown whether a promoter from one species could effectively drive expression of a protein coding sequence from a second species in the mammary gland of a third species. (JE005 at 3-4, ¶9.) Dr. Strijker's testimony is also consistent: as of 1986, "it had not been determined which, if any promoters, were suitable for the task, and what if any other regulatory sequences might be required to achieve expression in milk." (JE007 at 3, ¶7.) We conclude from these statements that as of 1986, there was little empirical evidence relating to the efficacy of promoters taken from one species used in another. Thus, there was, as of the critical date, little if any basis for predicting the results of linking different regulatory sequences to other protein coding sequences.

Particularly relevant to the status of the WAP promoter, Dr. Meade states that whey acid protein is specific to rodents, and is not normally present in the milk of ruminants. (JE007 at 3, ¶7.) Moreover, Dr. Meade states that there was no evidence that the WAP promoter would function in bovines (*id.*), and that, in 1986, he thought it would have been more likely that a milk promoter from a ruminant would facilitate expression of

heterologous proteins in ruminant milk. (*Id.* at ¶8.) Dr. Meade's statements are supported by Dr. Strijker's description of the Campbell & Rosen reference (JE009), that this reference reported that the WAP promoter had a "very unusual TATA box." (JE005 at 4, ¶9.) Dr. Strijker's statement that it was well-known that mutations of a highly conserved TATA regulatory sequence about 30 base pairs upstream from the transcription start site resulted in "severe reduction of transcription levels" (*id.* at 2, ¶6), supports his conclusion that the unusual TATA sequence implies that either the WAP promoter was "inherently extremely weak, and/or that the WAP promoter was regulated in a manner not yet known and probably requiring one or more additional sequences besides the TATA box and the CAAT region." (*Id.* at 4, ¶9.) The conclusions of Drs. Meade and Strijker are supported by the Rosen et al. reference, published March 30, 1986 (JE010), reporting the failure to observe WAP gene expression in the majority of transfectants analyzed. We find that the weight of the evidence is that the WAP promoter was known to be unusual, and that it was known that there were difficulties using it for heterologous protein expression in mammary gland cells.

Against this background of the state of the art, we find that, taken as prior art, DeBoer's involved claims reciting the use of promoters generally would not have provided one of ordinary skill in the art with a suggestion, reason, or

motivation, or a reasonable expectation of success, to use the WAP promoter recited in Gordon's involved claims. Thus, we hold that Gordon's claims would not have been anticipated by, or obvious over, DeBoer's claims; in other words, the claims of the two parties are not drawn to the same patentable invention. Accordingly, we find, acting on behalf of the Director of the United States Patent and Trademark Office, that there is no interference-in-fact.

Order

In consideration of the joint motion for no interference in fact, it is:

ORDERED that the joint motion that there is no interference-in-fact between any of junior party DeBoer's U.S. Patents Nos. 5,741,957, 6,013,857, and 6,140,552, and senior party Gordon's application 08/246,259 is GRANTED;

FURTHER ORDERED that a copy of this judgment shall be given a number and entered in the administrative files of Junior Party DeBoer's U.S. Patents Nos. 5,741,957, 6,013,857, and 6,140,552;

FURTHER ORDERED that a copy of this judgment shall be given a number and entered in the administrative file of senior party Gordon's application 08/246,259;

FURTHER ORDERED that senior party Gordon's application 08/246,259 shall be returned to the examiner for further proceedings not inconsistent with this order;

FURTHER ORDERED that if there is a settlement agreement, attention is directed to 35 U.S.C. § 135(c) and 37 C.F.R. § 1.661.

RICHARD E. SCHAFER Administrative Patent Judge	BOARD OF PATENT APPEALS AND INTERFERENCES
RICHARD TORCZON Administrative Patent Judge	
MARK NAGUMO Administrative Patent Judge	INTERFERENCE TRIAL SECTION

Attorney for Deboer
(real party in interest:
Pharming, B.V.)

Edward J. Keeling, Esq.
Steven W. Parmelee
Mark Sandbaken
TOWNSEND AND TOWNSEND AND CREW, LLP

Attorney for Gordon
(real parties in interest:
Genzyme Corp., and United States of America
as represented by the National Institutes of Health)

Paul T. Clark, Esq.
CLARK & ELBING LLP

Backup Counsel
Richard Wagner
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.