United States Court of Appeals for the Federal Circuit

01-1169

(Interference No. 103,324)

MICHAEL J. ADANG and JOHN D. KEMP,

Appellants,

v.

DAVID A. FISCHHOFF and STEPHEN G. ROGERS,

Appellees.

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Roger W. Parkhurst, Parkhurst & Wendel, L.L.P., of Alexandria, Virginia, argued for appellees. With him on the brief was Charles A. Wendel. Of counsel on the brief was Thomas P. McBride, Jr., Monsanto Company, of St. Louis, Missouri.

Appealed from: Patent & Trademark Office
Board of Patent Appeals and Interferences

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MICHAEL J. ADANG and JOHN D. KEMP,

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DAVID A. FISCHHOFF and STEPHEN G. ROGERS,

Appellees.

DECIDED: April 10, 2002

Before GAJARSA, Circuit Judge, FRIEDMAN, Senior Circuit Judge, and LINN, Circuit Judge.

LINN, Circuit Judge.

Appellants seek review of the final decision of the Board of Patent Appeals and Interferences (the "Board") in Interference 103,324 construing Count 1 and, based on this count construction, finding Application 06/848,733, filed on April 4, 1986, by Dr. Michael J. Adang and Dr. John D. Kemp (collectively "Adang"), to be nonenabling, and finding that Adang had not shown actual reduction to practice prior to Fischhoff's November 20, 1986, priority date. Fischhoff v. Adang, Interference No. 103,324 (Bd. Pat. Appeals & Interferences Sept. 29, 2000) ("Board opinion"). Because the Board erred as a matter of law in its count construction, and because Application 06/848,733 is nonenabling even under the correct count construction, and thus is not determinative on priority, we affirm in part, reverse in part, and remand to the Board for further proceedings, consistent herewith, under the correct count

construction.

I. BACKGROUND

A. Overview of the Technology

This interference involves tomato plants that have been genetically modified to incorporate a bacterial gene that confers insect resistance. The gene is derived from a strain of the soil-dwelling bacterium Bacillus thuringiensis ("Bt"), which produces one or more crystal proteins that are highly toxic to certain insects. These proteins vary in size and amino acid sequence, but all are originally produced by the bacterium as a protoxin, or inactive form, which is aggregated during the sporulation stage of the bacterial lifecycle to form crystals. When the spores are eaten by an insect, the protoxin is activated by the alkalinity and enzymes of the insect gut. This involves the cleavage of the protoxin into two portions, one or both of which are in the "activated" state that is toxic to the insect ("toxin form"). The activated toxin dissolves the stomach lining of the insect, causing it to die. As a result of this cleavage, the protoxin form differs from the toxin form in molecular weight: while the protoxin has a molecular weight of about 130 kD, the activated toxin form has a molecular weight of about 67 kD.

The procedure used to insert the Bt gene into plant cells (termed "transformation") and generate genetically modified plants from the transformed cells (termed "regeneration") is as follows. The gene encoding a Bt protein is initially isolated from a strain of the bacterium and is inserted into a circular piece of DNA termed a "plasmid." Plasmids are small loops of DNA that can be used to transfer a gene of interest between biological systems.

The isolated Bt gene is then transferred to a modified plasmid derived from Agrobacterium tumefaciens, a soil-dwelling bacterium often used in the transformation of plants. This bacterium has a natural ability to inject DNA into the genome of plant cells via

plasmids, termed Ti plasmids, that carry genes that can cause tumor formation in plants. The modification of this Ti plasmid is carried out by replacing the tumor-forming genes in the Ti plasmid with foreign genes of interest. By doing this, the modified Ti plasmid is rendered capable of stably integrating into the genome of a host plant and importing the traits of the foreign genes it carries into the host plant.

One important element in such a modified Ti plasmid is a DNA sequence, termed a "promoter," that directs the production of a messenger RNA ("mRNA") copy of the foreign gene (a process known as "transcription"). This mRNA then serves as a template for the production of a growing chain of amino acids that comprise the protein encoded by the gene (a process known as "translation"). The promoter sequence is the site where the cellular transcription machinery initially forms and binds to the DNA.

After the modified Ti plasmid bearing the Bt gene has been produced, it is returned to the Agrobacterium, and a population of these modified bacteria is then brought into contact with tomato cells. The cells are incubated together with the bacteria to allow for the transformation of the cells with the Bt gene. The transformed cells are then cultured to create regenerated tomato plants that produce a Bt crystal protein.

B. Adang's Alleged Conception and Reduction to Practice

Adang alleged the following sequence of events. In 1982, Adang conceived of the idea of genetically modifying plants such that a Bt crystal protein gene would be expressed in plant tissues at levels insecticidal to Lepidopteran insects. In September 1983, Adang succeeded in placing the full length gene (that is, the gene encoding the larger protoxin) into a bacterial expression vector (a DNA molecule allowing the bacterium to express the gene, thus producing protein), which allowed Adang to confirm that the gene had been isolated and

actually expressed a protoxin of approximately 130 kD that was insecticidal when eaten by a Lepidopteran insect. By March of 1984, this full length gene had been placed under the control of a promoter sequence allowing expression of the gene by a plant (a "plant-expressible" promoter). By March of 1985, the full length gene and the plant-expressible promoter had been placed into an Agrobacterium vector, and by July of that year, several lines of transformed tomato cells had been developed. Assays in March of 1986 confirmed the production of a Bt crystal protein in the tomato plants regenerated from the transformed cells. Bioassays conducted prior to June 12, 1986, showed that the plants were toxic to Lepidopteran insect larvae.

C. Procedural History

On June 10, 1991, Adang filed Application 07/713,624 ("Adang '91") entitled "Insect Resistant Plants" and directed to the above invention. This application claimed benefit under 35 U.S.C. § 120 of the October 21, 1988, filing date of continuation-in-part Application 07/260,574 ("Adang '88"), the April 4, 1986, filing date of continuation-in-part Application 06/848,733 ("Adang '86"), and the September 26, 1983, filing date of Application 06/535,354 ("Adang '83").

On December 23, 1991, Dr. David A. Fischhoff and Dr. Stephen G. Rogers (collectively "Fischhoff") filed Application 07/813,250 ("Fischhoff '91") entitled "Insect Resistant Tomato Plants," claiming benefit under 35 U.S.C. § 120 of the November 20, 1986, filing date of Application 06/932,818 ("Fischhoff '86").

On February 28, 1994, an Administrative Patent Judge ("APJ") declared this interference between the subject matter claimed in Adang '91 and Fischhoff '91. Count 1 of the interference reads as follows:

> A tomato plant which has been regenerated from a tomato plant cell transformed to comprise a full length Bacillus thuringiensis crystal protein gene capable of encoding a Bacillus thuringiensis crystal protein of about 130 kD under control of a promoter such that said gene is expressible in said plant in amounts insecticidal to Lepidopteran insects.

For the subject matter of count 1, the APJ accorded Adang benefit of the October 21, 1988, filing date of Adang '88, and the April 4, 1986, filing date of Adang '86, and accorded Fischhoff benefit of the November 20, 1986, filing date of Fischhoff '86.

On September 29, 2000, the Board issued a Final Decision in the interference. In its decision, the Board construed Count 1 to require that "the tomato plants must produce Bt crystal protein having a molecular weight of ~130 kD in amounts sufficient to destroy or control Lepidopteran insects." Board opinion, slip op. at 15 (emphasis added). Specifically, the Board held that

> tomato plants encompassed by Count 1 (1) must have been regenerated from a tomato plant cell transformed by a full length Bt crystal protein gene which encodes Bt crystal protein of about 130 kD under control of a promoter which directs expression of said structural gene in said tomato plant cell, and (2) must produce amounts of Bt crystal protein protoxin of about 130 kD which destroy or control Lepidopteran insects in any way.

Board opinion, slip op. at 19. Thus, under the Board's count construction, it is insufficient to show merely that the full length gene which is capable of encoding the Bt crystal protein protoxin is incorporated into the tomato plant genome and that the resulting plants are toxic to Lepidopteran insects; rather, the toxic effects must be directly attributable to "Bt crystal protein protoxin of about 130 kD" that is actually produced by the transformed plants in "amounts . . . which destroy or control Lepidopteran insects in any way."

In light of this count construction, the Board considered Fischhoff's motion to deny Adang the benefit of the April 4, 1986, filing date of Adang '86. The Board accordingly

considered both the adequacy of the written description of Adang '86 and whether that disclosure would have enabled those of skill in the art to practice the invention of the count without undue experimentation.

The Board found that Adang '86 did contain an adequate written description, in that it

> (1) describes transformed foreign plant cells using Bt crystal protein genes which encode known Bt crystal proteins which are toxic to Lepidopteran insects under control of a promoter, (2) provides an example . . . said to show the successful transformation of cells of at least one of the 94 kinds of plants recommended for protection by Bt insecticidal protein, namely tobacco, by a full length Bt crystal protein gene which encodes a Bt crystal protein of about 130 kD which is toxic to Lepidopteran insects, and (3) describes at least 94 kinds of plants which may be protected by Bt insecticidal proteins, including tomatoes, each of whose plant cells are said to be capable of being transformed by Bt crystal protein genes which encode Bt crystal proteins which are toxic to Lepidopteran insects.

Board opinion, slip op. at 37-38.

However, the Board held that Adang '86 lacked an enabling disclosure. The question presented was whether one of skill in the art would have been able to practice the invention of the count without undue experimentation. Here, the Board focused on the difference between the transformed tobacco plant which was the subject of the embodiments of Adang '86 and the tomato plant, which was merely listed in the patent disclosure along with numerous other plants which were potential subjects of similar transformations. In finding Adang '86 not enabling, the Board relied on several sources of evidence.

First, in response to experimental evidence attacking Adang's example based on the allegedly inherent variability of different bioassays, Adang had earlier argued that the experiments were "invalid because [the experimenter] used a completely different strain of tobacco from the strain Adang used in Adang's Example." Board opinion, slip op. at 42. The Board found that this

> indicates that persons skilled in the art would not have expected success in regenerating tomato plants insecticidal to Lepidopteran insects from dicotyledonous tomato plant cells transformed by a full length Bt crystal protein gene based on evidence that tobacco cells had been successfully transformed by the same genetic construct and one strain of dicotyledonous tobacco plants insecticidal to Lepidopteran insects had been regenerated therefrom.

Id. at 43.

Second, the Board found that the Vaeck, et al., European Patent Application 193,259, published September 3, 1986 ("DeGreve"), taught that expression of foreign genes in transformed plant cells "is by no means straightforward" and that "the successful transformation of plant cells using vectors . . . is not necessarily predictable prior to attempting a desired transformation." Board opinion, slip op. at 43-44. Furthermore, the Board found that this disclosure indicated that genetically engineering plant cells to express "the Bt2 polypeptide" was "far more difficult than other genes" because of the large size of the protein even in its truncated toxin form, the particular properties, such as solubility, of the protein, potential toxic effects of the protein on the plant cells themselves, and difficulties in ensuring that the protein expressed in plant cells had the same properties as that synthesized in bacteria. Id. at 44. The Board found that this reference, despite extensive engineering specifics, examples and results, "merely contemplate[d] future success." Id. at 46.

Next, the Board considered a 1985 Gene article authored by Adang ("Adang Gene"). The Board quoted the following passage, finding it "most pertinent" to the legal issues presented:

> E. coli pBT73-16 contains a complete crystal protein gene, yet peptides were observed ranging from the expected 133 kDal to 68 kDal. One explanation for this range in peptide sizes is that the translation product is not stable in E. coli but is proteolytically cleaved to a relatively stable 68-kDal peptide. An alternative explanation is that premature termination of transcription or translation could be occurring . . . .

Board opinion, slip op. at 48. The Board made three findings based on this excerpt. First, the Board found that it showed that one skilled in the art reasonably could not have predicted whether any promoter sequence "would direct expression of a full length Bt crystal protein gene which encodes a Bt crystal protein of about 130 kD in a foreign host cell transformed by said full length Bt crystal protein gene and production of a Bt crystal protein of about 130 kD by said foreign host cell." Id. Second, the Board found that this showed that one of skill in the art could not have predicted that any selected promoter sequence would achieve "production of Bt crystal protein of about 130 kD in amounts capable of destroying or controlling Lepidopteran insects." Id. Third, the Board found that the reference showed that "evidence that a foreign host cell transformed by a Bt crystal protein gene which encodes a Bt crystal protein of about 130 kD, produces a Bt crystal protein which is toxic to Lepidopteran insects does not establish that the foreign host cell has produced insecticidal amounts of a Bt crystal protein of about 130 kD." Id. at 48-49.

The fourth reference the Board relied on was a 1987 Nature article by Vaeck, et al., entitled "Transgenic plants protected from insect attack." Based on the statement in the article that "for the promoter gene constructs we used, only truncated bt2 genes give rise to expression levels that are strongly insecticidal in transgenic tobacco," Board opinion, slip op. at 50, the Board found that this showed "how very critical the choice of the control promoter is to production of the full length bt2 crystal protein gene in amounts insecticidal to Lepidopteran insects." Id. Furthermore, the Board noted that Vaeck stated that "[w]hy the complete bt2 gene is not expressed at an equally high level in plant cells, is not known. Several parameters, such as differential RNA stability and translation efficiency might be important." Id. at 51.

Furthermore, Vaeck also reported no success using "intact bt2 coding sequence," id., and predicted that higher levels of toxin "might be achieved" in the transformed plants "using chimeric Bacillus genes containing stronger plant-specific promoters." Id. at 52. Based on these excerpts, the Board found that "Vaeck's report of the state of the art in 1987 [was] an invitation to experiment rather than a report of success," and that "Vaeck's view of the state of the art . . . [was] far more substantiated and credible than is the view Adang's Brief for Final Hearing presents." Id.

Finally, the Board relied on a 1987 Plant Physiology article by Barton et al. The Board noted that this reference taught that "[a]nalysis of the expression of the chimeric [Bt] gene in the [insect-]resistant [tobacco] plants has revealed several problems which affect the levels of toxin gene expression." Board opinion, slip op. at 53. Barton found that tobacco calli (masses of relatively undifferentiated cells) containing the intact Bt protoxin died and concluded that the expression of the protein itself was lethal to the plant cells. Id. at 53-54. Even the use of the truncated gene, that is, a gene encoding the truncated toxin form of the protein, was not fully satisfactory, since "the level of toxin mRNA obtained in our insect-resistant transformants remained quite low." Id. at 54. Furthermore, Barton indicated that the analysis was ongoing and predicted that "[a] detailed analysis of the present toxin gene expression . . . will provide insight into problems specific to the expression of toxin protein in plants." Id. at 55.

The Board found that the combination of Adang's tobacco strain distinction argument, coupled with the other contemporaneous references, raised "substantial doubts" that Adang '86 would have enabled those of skill in the art to practice the invention embodied in Count 1 as of the April 4, 1986, filing date. The Board held that

> the factors and problems . . . were so numerous and misunderstood, and

> success in transforming tobacco plant cells to express a full length Bt crystal protein gene . . . was so rare and unpredictable, that persons skilled in the art having the disclosure of Adang '86 before them, even with one example of tobacco plant cell transformation, reasonably would not have expected to be able to successfully transform tomato plant cells by the same procedure to express a full length Bt crystal protein gene encoding Bt crystal protein of about 130 kD and regenerate tomato plants which produce Bt crystal protein of about 130 kD in amounts which destroy or control Lepidopteran insects therefrom, without undue experimentation.

Board opinion, slip op. at 55-56. The Board found that its legal conclusion was bolstered by the fact that Adang '86 simply identified total Bt crystal protein without identifying molecular weight, since under the Board's construction it was necessary to tie insect toxicity directly to the presence of the 130 kD protoxin form of the protein. Id. at 56-57.

Furthermore, the Board found that Adang had not established a priority date earlier than November 20, 1986, the filing date of Fischhoff '86, based either on actual reduction to practice or prior conception plus diligence in reduction to practice. The Board based this conclusion primarily on its determination that Adang had not established "reduction to practice of tomato plants which produce Bt crystal protein of about 130 kD in amounts effective to destroy or control Lepidopteran insects." Id. at 108 (emphasis added).

II. DISCUSSION

A. Standard of Review

> Patent interference count construction is a matter of law. Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 500, 42 USPQ2d 1608, 1612 (Fed. Cir. 1997); DeGeorge v. Bernier, 768 F.2d 1318, 1321, 226 USPQ 758, 760 (Fed. Cir. 1985). This court reviews the Board's count construction de novo. Credle v. Bond, 25 F.3d 1566, 1571, 30 USPQ2d 1911, 1915 (Fed. Cir. 1994). The court must look at the language of the count as a whole and consider the grammatical structure and syntax. Genentech, 112 F.3d at 500, 42 USPQ2d at 1612. Express limitations in counts may not be ignored. Hitzeman v. Rutter, 243 F.3d 1345, 1354, 58 USPQ2d 1161, 1167 (Fed. Cir. 2001) (citing McBride v. Teeple, 109 F.2d 789, 799, 44 USPQ 523, 533 (CCPA 1940)).
> Enablement is a question of law and is reviewed de novo. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Priority, conception, and reduction to practice are

questions of law which are based on subsidiary factual findings. Cooper v. Goldfarb, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998). The Board's findings of fact supporting legal conclusions are reviewed for substantial evidence. In re Gartside, 203 F.3d 1305, 1315, 53 USPQ2d 1769, 1775 (Fed. Cir. 2000).

B. Analysis

1. Count Construction

Count 1 of the interference reads as follows:

> A tomato plant which has been regenerated from a tomato plant cell transformed to comprise a full length Bacillus thuringiensis crystal protein gene capable of encoding a Bacillus thuringiensis crystal protein of about 130 kD under control of a promoter such that said gene is expressible in said plant in amounts insecticidal to Lepidopteran insects.

As noted above, the Board's count construction requires not only that the full length gene which is capable of encoding the Bt crystal protein protoxin be incorporated into the tomato plant genome and that the resulting plants be toxic to Lepidopteran insects, but also that the toxic effects be directly attributable to the presence of the 130 kD protoxin protein, which must be actually produced by the transformed plants in amounts that destroy or control the insects.

In its analysis, the Board first looked to the language of the count as a whole, in accordance with Genentech, Inc. v. Chiron Corp., 112 F.3d at 500, 42 USPQ2d at 1612 (holding that in construing the count, the court "must look at the language as a whole and consider the grammatical structure and syntax"). The Board stated that the full length gene of the count "encodes a Bt crystal protein which (1) must have a molecular weight of 'about 130 kD', and (2) must be insecticidal to Lepidopteran larvae in the amounts produced by tomato plants regenerated from cells transformed by the full length Bt crystal protein gene." Board opinion, slip op. at 11. Finding the count to be ambiguous, the Board next looked to the specifications at issue for guidance in construing the terms of the count, in accordance with DeGeorge v. Bernier, 768 F.2d 1318, 1321-22, 226 USPQ 758, 761 (Fed. Cir. 1985) (holding that "resort to the specification is necessary only when there are ambiguities inherent in the claim language or obvious from arguments of counsel"). The Board found support for its

interpretation in both Adang ’86 and Fischhoff ’86, in the form of teachings distinguishing the 130 kD protoxin itself from the lower molecular weight toxin form, which the Board found was taught by Adang to result either from the expression of a truncated form of the Bt gene, or from the cleavage of the protoxin in the insect gut. Board opinion, slip op. at 11-12. The Board appears to have imported this distinction between the forms of the protein into its consideration of the full length gene; underlying its construction is an assumption that, when expressed, the full length gene of necessity produces the 130 kD protoxin, and that insect toxicity is solely attributable to the presence of this protoxin.

We hold that the Board erred in its construction of this count limitation. The Board was correct in determining that the language of the count was ambiguous; specifically, the limitation that “said gene is expressible in said plant” offers little guidance as to the form of the protein thereby produced. The Board, finding in the specifications a clear distinction between the full length and truncated genes, appears to have presumed that the product of the expression of the full length gene would be the 130 kD protoxin. However, the relevant limitation directed to the gene itself simply states that the gene is “capable of encoding” the 130 kD form. It is too great a leap to mandate that, in order to come within the scope of the count, expression of a gene “capable of encoding” a protein must be shown to produce only that protein.

The Board’s consideration of the record also overlooks the most damning evidence against its count construction. The Board’s construction resolves the ambiguity in a way that renders the count so narrow that no example of either Fischhoff or Adang satisfies the limitations of the count as construed by the Board.

For instance, Example 12 of Adang ’86 discloses the transformation of tobacco plant cells with the “Bacillus thuringiensis insecticide gene” and the expression of the gene in

tobacco plants regenerated from the transformed cells. The presence of the protein in the plant tissues was detected using an enzyme-linked immunosorbent assay ("ELISA") using a primary antibody "raised to B. thuringiensis HD73 crystal protein." The term "crystal protein" is stated in the specification "to refer to both the full length protoxin and toxin forms." Since it is unclear which form of the protein was used to raise the antibody, it was impossible to distinguish between the protoxin and toxin forms of the protein based on the ELISA results. Thus, although the results of the ELISA showed the presence of "crystal protein" in the tobacco leaf tissue, and bioassays showed that insect larvae that consumed the transformed tissue died, it was not clear from the results that the deaths were the result of "amounts of Bt crystal protein protoxin of about 130 kD which destroy or control Lepidopteran insects in any way." Board opinion, slip op. at 19 (emphasis added).

Similarly, Example 15 of Adang '88, which disclosed the transformation of tomato plants, also failed to disclose a direct connection between the insect mortality results of the bioassays and the presence of a specific amount of the 130 kD protoxin form of the protein. The ELISA testing suffered from the same specificity problems as in Example 12 of Adang '86. Although Western blotting (which can distinguish between proteins based on size) revealed the presence of both the protoxin and toxin forms of the crystal protein in the transformed tomato leaf tissue, the data presented for the total amount of protein in tissue samples is derived from the ELISA assay and encompasses both forms of the protein. Thus, since the amount of the 130 kD protoxin in the leaf tissue was not quantified, it is impossible to determine if the amount of the protoxin present was sufficient to "destroy or control Lepidopteran insects in any way."

Lastly, Fischhoff's examples also fail to satisfy the count as construed by the Board. Examples 2-9 of Fischhoff '86 disclose the construction of expression plasmids containing both full length and truncated crystal protein genes, and the transformation of tomato plants using those plasmids. However, there is no indication in these examples that the protein expressed in the plant tissue was assayed; rather, assays were conducted for mRNA transcribed from the crystal protein genes. There is accordingly no disclosure of the form of the protein (toxin or protoxin) produced in the transformed tissue and no connection shown between specific amounts of the 130 kD protoxin and insect toxicity, as required by the Board's construction.

We thus hold that it was error for the Board to construe Count 1 to require that the transformed tomato plants of the count "must produce amounts of Bt crystal protein protoxin of about 130 kD which destroy or control Lepidopteran insects in any way." (emphasis added). The language in the count to the effect that "said gene is expressible in said plant in amounts insecticidal to Lepidopteran insects," although somewhat ambiguous, is properly interpreted to mean that the full length gene incorporated into the tomato plant is expressed, thus producing some form of crystal protein, and that the amount of protein produced renders the plant toxic to Lepidopteran insects. We accordingly hold that tomato plants encompassed by Count 1: (1) must have been regenerated from a tomato plant cell transformed by a full length Bt crystal protein gene which encodes Bt crystal protein of about 130 kD under control of a promoter which directs expression of said structural gene in said tomato plant cell, and (2) must produce amounts of a Bt crystal protein of any size which destroy or control Lepidopteran insects in any way.

2. Enablement

The legal question of enablement involves an assessment of whether a patent disclosure would have enabled one of skill in the art at the time the application was filed to make and use the claimed invention without undue experimentation. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). In this case, to carry its burden, Fischhoff is required to show that Adang '86 did not enable one of skill in the art on April 4, 1986, to (1) transform tomato plant cells using a full length Bt crystal protein gene which encodes a known Bt crystal protein of 130 kD that is toxic to Lepidopteran insects, so that the tomato cells express this gene; (2) regenerate tomato plants from the transformed tomato cells, and (3) produce a Bt crystal protein in the tomato plants in amounts toxic to Lepidopteran insects, without undue experimentation. Although the Board found that Adang '86 did not enable Count 1, the Board erred in its count construction by requiring the insect toxicity of the transformed plants to be attributable to sufficient amounts of the 130 kD protoxin. Accordingly, we must determine whether the factual findings of the Board underlying its enablement determination were supported by substantial evidence and permit this court to reach a legal conclusion on enablement based on the correct count construction. We hold that the Board's factual findings underlying the Board's legal conclusion of nonenablement were supported by substantial evidence, and even under the correct count construction, those factual findings lead to the conclusion that Adang '86 did not enable Count 1. The Board's findings are addressed in detail below.

The Board found that Adang's argument distinguishing the experimental evidence because a different variety of tobacco was used indicated that those skilled in the art would not have expected success in transferring the technique to the even more different tomato plant without undue experimentation. This finding is supported by substantial evidence. Adang's

argument is predicated on the assumption that expression of the gene in one strain of tobacco cannot serve as a valid basis for concluding that similar expression will be achieved in a different strain. Adang seeks to characterize its argument as limited to the question of the variability of the bioassays performed. However, Adang's expert witness states that a part of that variability is the effect of the strain of tobacco on the expression of the crystal protein gene in the plant tissue. "If [the experimenter's] aim was to replicate Adang's experimental conditions, the reasonable starting point would have been to use the same . . . variety of plant to assure that the insect response and cellular expression conditions would replicate those of Adang." (emphasis added). If expression is not consistent among strains within a single species, as Adang's witness suggests, it is reasonable to conclude that those of skill in the art would not have expected expression in tomato plants to track that in a particular strain of tobacco. Accordingly, the findings of the Board in this regard were supported by substantial evidence.

The Board's findings with respect to the DeGreve patent application are also supported by substantial evidence. The Board accurately quoted this application's teaching that expression of foreign genes in transformed plant cells "is by no means straightforward. Various lines of evidence indicate that the level of expression of the foreign genes of non-plant origin not only varies greatly in different transformed tissues but are in general very low." This is followed in the DeGreve application by speculation as to the possible causes of the low level of expression. The authors conclude that "the successful transformation of plant cells using vectors . . . is not necessarily predictable prior to attempting a desired transformation." Furthermore, the specification plainly teaches that the Bt crystal protein itself created problems apart from those general to the expression of foreign genes in plants:

> Engineering of differentiated plant cells and their progeny to express the Bt2 polypeptide and/or a truncated version thereof . . . is far more difficult than other genes such as antibiotic resistance genes or other plant genes such as thaumatin due to one or more of the following: (1) the large size of the Bt2 toxin, even in its truncated form; (2) the particular properties of the Bt2 polypeptide (such as, but not limited to, solubility of the polypeptide); (3) the potential toxicity of the Bt2 polypeptide toward the plant cells; or (4) the Bt2 polypeptide synthesized in plant cells and their progeny must retain substantially the same properties as the crystal protein synthesized in bacteria.

Board opinion, slip op. at 44. Adang argues that, when considered as a whole, this reference indicates the feasibility of the method, pointing to the working examples in tobacco that are disclosed. However, as to other plant species such as tomato, the specification contains no more than a belief that the method might be of use: "[t]he present invention contemplates that the hybrid plasmid transformation vectors may be used to develop plant cells . . . exhibiting insect resistant properties. It is contemplated that plants, particularly dicotyledonous plants, other than those described below in the examples can be transformed such as cotton, sugarbeet, soybean, rape . . . ." (emphasis added). In view of the earlier teaching of the same specification that transformation of such other plant species was not predictable, however, the Board's finding that this reference "merely contemplates future success" was supported by substantial evidence.

The 1985 Adang Gene article describes experiments in which both full length and truncated Bt crystal protein genes were transferred into a host bacterium (Escherichia coli) and encoded proteins were expressed. The Board found that this reference established that one of skill in the art could not have predicted whether any select promoter sequence would have directed production, in a foreign host cell, of the 130 kD protoxin from the full length gene, or that this protoxin would have been present in amounts toxic to Lepidopteran insects. The Board also found that a showing of insect toxicity in a transformed cell was not sufficient to

establish that the cell had produced the 130 kD protoxin in toxic amounts. Although these findings are supported by substantial evidence in the Adang Gene article, they focus on the distinction between the toxic effects attributable to the 130 kD protoxin versus those attributable to the shorter toxin. As we have explained above, this distinction is meaningless in light of the correct count construction; insect toxicity attributable to either the toxin or protoxin, or both, suffices for Count 1.

The Vaeck Nature reference, published July 2, 1987, describes the transformation of tobacco plants using both full length and truncated Bt crystal protein genes, the expression of the crystal proteins in those plants, and the resulting insect toxicity. The Board found this reference to be "an invitation to experiment rather than a report of success." Board opinion, slip op. at 52. The disclosure indicated to the Board that "the art of expressing a full length Bt crystal protein gene which encodes Bt crystal protein under control of any select promoter in tobacco cells, not to mention tomato cells, in amounts insecticidal to Lepidopteran insects was highly unpredictable." Id. at 51. These findings are supported by substantial evidence. Although Vaeck used the full length Bt crystal protein gene in the experiments, the plants transformed with this gene showed no greater insect toxicity than the control plants: "for the promoter gene constructs we used, only truncated bt2 genes give rise to expression levels that are strongly insecticidal in transgenic tobacco." Vaeck stated that the reason for this failure to express the full gene was "not known," and speculated that "[s]everal parameters, such as differential RNA stability and translation efficiency might be important." Furthermore, the Board's finding that Vaeck showed "how very critical the choice of the control promoter is to production of the full length bt2 crystal protein gene in amounts insecticidal to Lepidopteran insects," Board opinion, slip op. at 50, is supported by Vaeck's disclosure of failure to express

the full length gene using the promoters selected, and by Vaeck's speculation that "higher levels of expression . . . might be achieved using chimaeric Bacillus genes containing stronger plant-specific promoters." (emphasis added). The Board found that "Vaeck's view of the state of the art in 1987 is far more substantiated and credible than is the view Adang's Brief for Final Hearing presents of the state of the art prior to 1987 . . . ." Id. at 52. We see no reason to disturb this credibility determination.

The final contemporary reference considered by the Board was the Barton, et al. Plant Physiology article, published in 1987. This reference also reports the results of experiments in which tobacco was transformed with both full length and truncated Bt crystal protein genes. However, Barton reported even less success than Vaeck with the full length gene: "we obtained tobacco calli that were shown by immunoblots to contain significant levels of intact protoxin . . . . However, all such calli soon became necrotic and died . . . . We eventually concluded that expression of intact [crystal protein protoxin] was lethal to plant cells." Barton reported success only with truncated forms of the gene and indicated that further study into methods of improving expression of the gene "will provide insight into problems specific to the expression of toxin protein in plants." (emphasis added).

In addition, both Adang and Fischhoff submitted expert testimony and experimental evidence on the issue of enablement. The Board found that the views of Adang's experts were "necessarily influenced by experimentation performed after 1986 and knowledge acquired therefrom, i.e., hindsight." Board opinion, slip op. at 60. After considering the evidence submitted by both sides, the Board concluded that

> because it is most consistent with essentially contemporaneous disclosures of the 1985-1987 publications discussed previously, including Adang's own 1985 publication (Adang Gene), we find the testimony and experimental evidence

> submitted in support of Fischhoff's view that the art was substantially unpredictable on April 4, 1986 more credible than the testimony and experimental evidence submitted by Adang's declarants.

Id. at 61. This determination was supported by substantial evidence and we see no reason to disturb it.

It is well settled that "omission of minor details does not cause a specification to fail to meet the enablement requirement." Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997). However, the gaps in the disclosure of Adang '86 amount to far more than minor details. As the Board found, this was a "substantially unpredictable" art as of the filing date. This finding was unsurprising in view of the record evidence that different groups of researchers employing the full length crystal protein gene achieved a broad spectrum of results in their attempts to transform tobacco plants and achieve insect toxicity, from abject failure and plant death (Barton) to apparent success (DeGreve). The factual findings of the Board, supported by substantial evidence, show that as of the filing date of Adang '86, disclosure of a successful transformation of tobacco plants using a full length Bt crystal protein gene and insect toxicity of those plants would not have enabled one of skill in the art at the time to successfully conduct the transformation of an entirely different species such as tomato. These deficiencies are not cured by the reference to a general method for transformation of tomato included in Adang '86. A successful transformation of tomato based on Adang '86 and the knowledge of one of skill in the art at the time would, in other words, have required undue experimentation. Accordingly, we affirm the Board's conclusion that Adang '86 did not enable the invention of Count 1 and that Adang is, therefore, not entitled to claim priority to the April 4, 1986, filing date of that application.

3. Priority

Since Adang '86 is not enabling, Adang's case for priority of invention of Count 1 rests on an ability to show that Adang had either actually reduced to practice an embodiment of the count prior to the November 20, 1986, filing date of Fischhoff '86, or had conceived of an embodiment of the count prior to that date and was diligent in reducing the embodiment to practice. As the presumptive junior party, Adang had the burden to show priority of invention by a preponderance of the evidence. Scott v. Finney, 34 F.3d 1058, 1061, 32 USPQ2d 1115, 1117 (Fed. Cir. 1994). The factual findings of the Board are insufficient to determine whether Adang has sustained his burden of proof on this issue.

The Board's factual findings focused on Adang's failure to show that the 130 kD crystal protein protoxin was expressed in the transformed plants. Thus, for example, the Board found that the bioassays in Adang '88 "test for toxic Bt crystal protein produced by the plants, not how much 130 kD crystal protein the plants produced." Board opinion, slip op. at 99. As noted above, however, under the correct construction of Count 1 it is immaterial which form of the crystal protein is produced, so long as it is clear that the protein results from the expression of the full length Bt crystal protein gene, which is "capable of encoding a . . . crystal protein of about 130 kD." (emphasis added). In other words, the toxic protein must not be the result of the expression of a truncated gene, which would not be capable of encoding the full 130 kD protoxin.

The Board's factual findings on this point are somewhat confused. On the one hand, the Board seems to settle the identity of the gene incorporated in the plasmid used to transform the tomato plants: "In our view, the evidence shows that Adang transformed tomato cells using a pH450 vector which includes a full length Bt crystal protein gene encoding Bt crystal protein of about 130 kD." Board opinion, slip op. at 104. On the other hand, the Board

expresses some doubt as to whether the tomato plants incorporated the entirety of this gene. "[T]he tomato plant cells may have been transformed by the full length Bt crystal protein gene which encodes Bt crystal protein of about 130 kD and/or a truncated fragment thereof." Id. at 104-05 (emphasis added). The Western blot evidence that the Board cites from Adang '88, furthermore, is unclear; although the specification states that "[b]oth protoxin and toxin was observed in leaf tissues," Western blot results for two transformants showed "smearing at about 110 kD." In other words, the assay failed to show any of the 130 kD protoxin in plants regenerated from those two transformants. Although Adang argues that all limitations of the count were met at the latest by June 12, 1986, on which date bioassays were allegedly conducted which showed that tomato plants transformed with the full length Bt crystal protein gene were toxic to Lepidopteran insects, we are unable to confirm this from the record on appeal.

Accordingly, we remand this matter to the Board for further consideration of the issue of priority.

III. CONCLUSION

The Board erred in construing Count 1 by requiring the insecticidal effect of the transformed tomato plants of the count to be attributable solely to sufficient amounts of the 130 kD Bt crystal protein protoxin. It is sufficient that the crystal protein that produces the insecticidal effects in the plants of the count be the result of the expression of the full length crystal protein gene; the size of the resulting protein is immaterial. Accordingly, we reverse the Board's count construction in this regard. The factual findings of the Board on the question of whether Adang '86 would have enabled persons skilled in the art to make and use the transformed tomato plants of the count as of the filing date of the application are supported by

substantial evidence. Even under the modified count construction, these findings indicate that undue experimentation would have been required to produce the tomato plants of the count on the basis of the disclosure of Adang '86. We thus affirm the Board's legal conclusion that Adang '86 was not an enabling disclosure and that Adang was not entitled to rely on the April 4, 1986 filing date of that application to establish priority. Finally, we are unable to determine on the basis of the record on appeal whether Adang established entitlement to a priority date before November 20, 1986. Accordingly, we remand the case to the Board for further consideration of this issue in light of the modified count construction.

COSTS

No costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, AND REMANDED