United States Court of Appeals for the Federal Circuit

(Serial No. 10/082,772)

IN RE PETER DROGE, NICOLE CHRIST, AND ELKE LORBACH

2011-1600

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences.

Decided: September 21, 2012

JONATHAN S. FRANKLIN, Fulbright & Jaworski L.L.P., of Washington, DC, argued for appellants. With him on the brief were STEVEN L. HIGHLANDER and SHEILA KADURA, of Austin, Texas.

MARY L. KELLY, Associate Solicitor, United States Patent and Trademark Office, of Alexandria, Virginia, argued for the Director of the United States Patent and Trademark Office. With her on the brief were RAYMOND T. CHEN, Solicitor, and KRISTI L. R. SAWERT, Associate Solicitor. Of counsel was AMY J. NELSON.

Before NEWMAN, MOORE, and O'MALLEY, *Circuit Judges*.

MOORE, *Circuit Judge*.

Peter Droge, Nicole Christ, and Elke Lorbach (collectively, Droge) appeal from the decision by the Board of Patent Appeals and Interferences (Board) affirming the rejection of claims 29, 30, 32-39, 43-51, and 58 of U.S. Patent Application No. 10/082,772 ('772 application) as obvious under 35 U.S.C. § 103. Because the Board correctly held that the claims would have been obvious over the prior art, we affirm.

BACKGROUND

The '772 application is directed to methods and compositions for recombining DNA in a eukaryotic cell (i.e., a cell with a nucleus), such as a human cell. The term "recombinant DNA" generally refers to DNA from one or more sources with a sequence that does not occur in nature. A process called "molecular cloning" is one way to create recombinant DNA molecules and direct their replication within a living host cell. This process involves inserting foreign DNA into a carrier, called a "vector," and then introducing the vector into a host cell. The vector can insert both its DNA and any foreign DNA into the host cell's DNA. When the host cell replicates, the vector with its foreign DNA also replicates. This allows for the production of a large quantity of the foreign DNA, which can be used in a wide variety of applications, such as production of recombinant proteins.

Viruses that infect bacteria, called bacteriophages, are commonly used as vectors. One well-known example is called "bacteriophage λ." In bacteriophage λ-based vector systems, a protein called "bacteriophage λ integrase" (or derivatives thereof) induces and facilitates DNA recombination. Naturally occurring (wild-type) bacteriophage λ integrase is called "Int."

One feature of bacteriophage λ that makes it a useful vector is its ability to perform sequence-specific recombination, which means that DNA may be inserted, deleted, or rearranged at a specific location on the target cell's DNA. Bacteriophage λ does this by using recognition sites, which are short sections of DNA that act as guideposts for the vector's insertion into the host cell's DNA. During recombination, the recognition site region of the vector's DNA will align with a complementary recognition site region on the host cell's DNA. The Int enzyme then cuts both the vector's and the host cell's DNA and facilitates insertion of the vector's DNA into the host cell's DNA. The DNA recognition sites used in bacteriophage λ-based vector systems are referred to as *attB*, *attP*, *attR*, and *attL*.

The Board affirmed the rejection of independent claim 29 of the '772 application, which the parties agree is representative of the claims on appeal, as obvious over the combination of U.S. Patent No. 6,143,530 (Crouzet) and an article by Christ & Droge (two of the three inventors of the '772 application). Claim 29 covers a method of recombining DNA in a eukaryotic cell using modified versions of wild-type Int. The particular Int mutants used in the claimed method are called Int-h and Int-h/218. The claimed recombination method is sequence-specific, facilitating recombination at either the *attB* and *attP* or the *attR* and *attL* recognition sites. Claim 29 recites:

> A method of sequence specific recombination of DNA in a eukaryotic cell, comprising:
>
> (a) *providing said eukaryotic cell*, said cell comprising a first DNA segment integrated into the genome of said cell, said first DNA segment comprising an [attB, attP, attL, or attR sequence or derivative thereof] . . . ;

> (b) introducing a second DNA segment into said cell . . . ;
>
> (c) further comprising *providing to said cell a modified bacteriophage lambda integrase Int*, wherein said modified Int is *Int-h or Int-h/218*, which induces *sequence specific recombination through said attB and attP or attR and attL sequences*.

'772 application, cl.29 (emphasis added).

The Crouzet reference discloses methods of making therapeutic DNA molecules using sequence-specific recombination either in a host cell or *in vitro*. Crouzet, col.3 ll.30-34, 59-61. Specifically, Crouzet discloses a method that uses bacteriophage λ and wild-type Int protein to insert a foreign DNA sequence into a host cell using the *attB* and *attP* recognition sites. *Id.* col.4 ll.21-52, col.5 ll.32-41. Crouzet also teaches that this method "may be carried out in any type of cell host," such as "bacteria or eukaryotic cells (yeasts, animal cells, plant cells)." *Id.* col.9 ll.48-60. Crouzet does not disclose use of modified integrases.

The Christ & Droge article discloses that the modified integrase proteins Int-h and Int-h/218 mediate sequence-specific recombination in prokaryotic cells (i.e., cells with no nucleus). This reference teaches that, compared to wild-type Int, the modified proteins Int-h and Int-h/218 have the advantage of an increased binding affinity for core binding sites present in the *att* regions. Christ & Droge also discloses that Int-h and Int-h/218 can perform recombination *in vivo* even in the absence of certain protein co-factors that assist with recombination, such as the integration host factor (IHF). IHF is present in prokaryotic cells but not in eukaryotic cells.

Based on the teachings of these references, the Board concluded that because "the wild-type integrase works in eukaryotic cells, the ordinary artisan would have had a reasonable expectation of success that [Int-h and Int-h/218] would also function at some level in eukaryotic cells." The Board considered a declaration from one of the inventors, Dr. Droge (Droge Declaration), which set out reasons why a person of ordinary skill in the art would not have had a reasonable expectation of success in using Int-h and Int-h/218 to induce recombination in eukaryotic cells. The Board, however, concluded that an article by Brenda J. Lange-Gustafson and Howard A Nash (Lange-Gustafson) refuted the assertions in the Droge Declaration. The Board thus held that claim 29 would have been obvious over the combination of Crouzet and Christ & Droge. Droge now appeals the Board's obviousness rejection of the '772 application claims. We have jurisdiction under 28 U.S.C. § 1295(a)(4).

DISCUSSION

Whether an invention would have been obvious under 35 U.S.C. § 103 is a question of law based on underlying findings of fact. *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). We review the Board's legal conclusions *de novo* and its factual findings for substantial evidence. *Id.* Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Id.* at 1312 (citation omitted).

Droge does not dispute that the Crouzet and Chris & Droge references, taken together, teach every limitation of the claimed method. Instead, Droge argues that a person of ordinary skill in the art would not have had a reasonable expectation of success in combining the teachings of these references. Specifically, Droge argues that Christ & Droge's disclosure of using the modified integrase proteins

Int-h and Int-h/218 to facilitate recombination in *prokaryotic* cells would not lead a skilled artisan to expect that these integrases would also work in *eukaryotic* cells. Droge contends that the Christ & Droge article teaches away from the claimed invention because it states that the recombinant activity of Int-h and Int-h/218 decreases in the absence of protein co-factors such as IHF, which are present in prokaryotic cells but not in eukaryotic cells.

Droge also argues that, even if the combination of Crouzet with Christ & Droge makes out a prima facie case of obviousness, the Droge Declaration rebutted it with additional evidence that a skilled artisan would not have had a reasonable expectation of success in using Int-h or Int-h/218 to recombine DNA in eukaryotic cells. The Droge Declaration explains that the ability of modified integrases to promote recombination in prokaryotic cells may be due to two features of those cells: (1) specific prokaryotic protein co-factors that assist with recombination, such as IHF; and (2) the particular three-dimensional structure of DNA in prokaryotic cells. The Droge Declaration states that it was not obvious that Int-h and Int-h/218 would work in eukaryotic cells because they had only been shown to work on DNA with the three-dimensional structure found in prokaryotic cells (negatively supercoiled). The declaration states that, at the time of invention, it was unclear whether these modified integrases would work on the topologically relaxed DNA in mammalian cells. Thus, Droge argues the Board's rejection should be reversed.

We conclude that substantial evidence supports the Board's determination that a person of ordinary skill in the art would have had a reasonable expectation of success when combining Crouzet and Christ & Droge. Crouzet discloses that wild-type bacteriophage λ integrase Int can induce site-specific DNA recombination using the

attB and *attP* recognition sites. Crouzet, col.4 ll.21-52, 32-41. Crouzet further discloses that wild-type Int can induce recombination in *both* prokaryotic and eukaryotic host cells, including animal cells. *Id.* col.9 ll.48-60 ("The method according to the invention may be carried out in any type of cell host. Such hosts can be, in particular, bacteria or eukaryotic cells (yeasts, animal cells, plant cells), and the like."). Although Crouzet does not teach the use of the modified integrases Int-h and Int-h/218, the Christ & Droge article supplies this missing element. Christ & Droge also supplies a motivation to use Int-h and Int-h/218 in the method taught in Crouzet—these modified integrases have increased affinity for core binding sites in the *att* regions, even in the absence of IHF. J.A. 773 ("Hence, Int-h/218 exhibits an enhanced ability to execute recombination on wild-type *att* sites in the absence of accessory factors IHF and Xis.").

The Lange-Gustafson article provides additional evidence in support of the Board's determination that a skilled artisan would have a reasonable expectation of success. Lange-Gustafson discloses that Int-h "sponsors reduced but significant levels" of recombination in the absence of IHF and that, "in the absence of IHF, Int-h recombines supercoiled and nonsupercoiled [DNA] identically." J.A. 889. The article *directly* contradicts the assertion in the Droge Declaration that a skilled artisan would not expect the modified integrases Int-h and Int-h/218 to work in eukaryotic cells based on the three-dimensional structure of DNA in those cells. Indeed, Lange-Gustafson states that Int-h recombines DNA "identically" regardless of whether its three-dimensional structure is supercoiled or topologically relaxed. The Christ & Droge article similarly concludes that neither supercoiling nor IHF are necessary. J.A. 769 ("Neither

supercoiling of *attP* nor the presence of IHF seems to be required for catalysis of these chemical reactions.").

These disclosures provide substantial evidence supporting the Board's finding that a person of ordinary skill in the art would have had a reasonable expectation of success for using the modified integrases disclosed in Christ & Droge in place of wild-type Int in the method taught in Crouzet. "Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). Because the references disclose that wild-type Int mediates recombination in eukaryotic cells and that Int-h and Int-h/218 can perform recombination even in the absence of IHF, the Board's fact finding that a skilled artisan would have had a reasonable expectation that Int-h and Int-h/218 would mediate recombination in eukaryotic host cells is supported by substantial evidence. Accordingly, we hold that the Board correctly concluded that the '772 claims at issue on appeal would have been obvious over the prior art. We have considered Droge's remaining arguments on appeal and find them to be without merit.

AFFIRMED