United States Court of Appeals for the Federal Circuit

00-1467

ELAN PHARMACEUTICALS, INC.
and ATHENA NEUROSCIENCES, INC.,

Plaintiffs-Appellants,

v.

MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH,

Defendant-Appellee.

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Appealed from: United States District Court for the Northern District of California

Judge William H. Alsup

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DECIDED: October 2, 2003

Before NEWMAN, GAJARSA, and DYK, Circuit Judges.

NEWMAN, Circuit Judge .

The initial opinion in this appeal, reported at Elan Pharmaceuticals, Inc. v. Mayo Foundation, 304 F.3d 1221, 64 USPQ2d 1292 (Fed. Cir. 2002), has been vacated, 314 F.3d 1299 (Fed. Cir. 2002) (en banc) and is replaced with this opinion and decision.

The United States District Court for the Northern District of California, granting the Mayo Foundation's motion for summary judgment of patent invalidity, held that Elan's two patents in suit, United States Patent No. 5,612,486 (the '486 patent) for "Transgenic Animals Harboring APP Allele Having Swedish Mutation," and Patent No. 5,850,003 (the '003 patent) for "Transgenic Rodents Harboring APP Allele Having Swedish Mutation," are invalid on the ground of anticipation by United States Patent No. 5,455,169 entitled "Nucleic Acids for Diagnosing and Modeling Alzheimer's Disease" (the Mullan reference).[1]

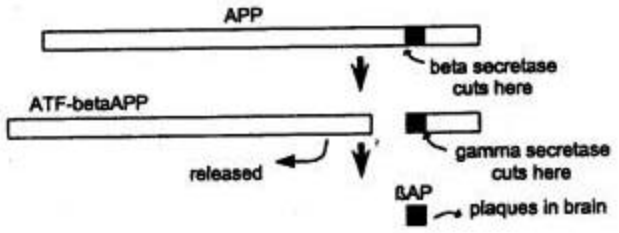
In response to the questions raised in the petitions for reconsideration, we clarify that invalidity based on anticipation requires that the assertedly anticipating disclosure enabled the subject matter of the reference and thus of the patented invention without undue experimentation. Applying this rule, we remand for determination of whether the Mullan reference was an enabling disclosure. The summary judgment is reversed, and the case is remanded for further proceedings.

BACKGROUND

At the time of the Elan invention it was known that the brains of people with Alzheimer's disease contain abnormal tangles and deposits of plaques, and that a principal component of the plaques is a protein fragment called beta-amyloid peptide or betaAP (also designated ßAP and Aß). The formation of betaAP in brain tissue is believed to induce or foster formation of Alzheimer's disease plaques.

It is believed that a mechanism by which betaAP is formed is the abnormal cleavage of a protein produced in brain cells, called the amyloid precursor protein (APP); and that this abnormal cleavage occurs when an enzyme produced in the brain, called beta-secretase, cleaves the APP molecule between amino acids 596 and 597; and a second enzyme produced in the brain, called gamma-secretase, releases the betaAP fragment from a portion of the cleaved APP. The mechanism is illustrated in the Elan brief as

Fig.1 - Processing of APP to ßAP and ATF-betaAPP



follows:

Humans who do not develop Alzheimer's disease are believed to break down the APP in a manner that does not form significant amounts of betaAP in the brain.

The Swedish mutation is an abnormal gene[2] that was discovered on chromosome 21 in a Swedish family that has an unusually high incidence of early-onset Alzheimer's disease. This mutation is described in the Mullan patent as a variation in the DNA nucleotides that encode codons 670 and 671, [3] wherein lysine and methionine, the amino acids normally encoded at these positions, are replaced with asparagine and leucine.

The Elan patents are directed to transgenic rodents whose genetic makeup has been modified to include the Swedish mutation. Claim 1 of the '486 patent is representative:

1. A transgenic rodent comprising
a diploid genome comprising a transgene encoding a heterologous APP polypeptide having the Swedish mutation wherein

the amino acid residues at positions corresponding to positions 595 and 596 in human APP695 are asparagine and leucine, respectively,
wherein the transgene is expressed to produce a human APP polypeptide having the Swedish mutation,
and wherein said polypeptide is processed to ATF-betaAPP in a sufficient amount to be detectable in a brain homogenate of said transgenic rodent.

Dependent claims add the limitations that the rodent is murine (mouse) and that the transgene is nonhomologously integrated.

The claims of the '003 patent differ only in that they include a promoter and a polyadenylation site. Claim 1 is representative:

1. A transgenic rodent comprising
a diploid genome comprising a transgene comprising in operable linkage a promoter, a DNA segment encoding a heterologous APP polypeptide and a polyadenlyation site,
wherein the APP polypeptide has the Swedish mutation whereby the amino acid residues at positions corresponding to positions 595 and 596 in human APP695 are asparagine and leucine, respectively,
wherein the transgene is expressed to produce a human APP polypeptide having the Swedish mutation,
and wherein said polypeptide is processed to ATF-betaAPP in a sufficient amount to be detectable in a brain homogenate of said transgenic rodent.

The Mullan reference was cited as prior art in prosecution of the Elan patents, and was distinguished upon amendment of the Elan claims to include the claim clause that refers to production of ATF-betaAPP in detectable amounts in the rodent brain.

I

The district court, granting Mayo's motion for summary judgment, held that the Mullan reference anticipates the Elan invention. Whether an invention is anticipated is a question of fact. Hoover Group, Inc. v. Custom Metalcraft, Inc., 66 F.3d 299, 302, 36 USPQ2d 1101, 1103 (Fed. Cir. 1995). On appeal, Elan requests review of the district court's determination that the Mullan reference anticipates the claims of the Elan patent because the Elan mouse is inherent in Mullan. We conclude that Elan's arguments are more properly characterized as enablement arguments rather than inherency arguments.

To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). See Bristol-Myers Squibb v. Ben Venue Laboratories, Inc., 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention."); PPG Industries, Inc. v. Guardian Industries Corp., 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). Review of Elan's opposition to Mayo's motion for summary judgment shows that, while Elan purports to contest Mayo's motion on the grounds that the Mullan patent does not inherently anticipate the Elan claimed mouse, the language and factual basis of this argument encompass enablement.

Enablement requires that "the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation." Minnesota Mining and Manufacturing Co. v. Chemque, Inc., 303 F.3d 1294, 1301, 64 USPQ2d 1270, 1278 (Fed. Cir. 2002); Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1369, 52 USPQ2d 1129, 1134 (Fed. Cir. 1999) ("Whether undue experimentation would have been required to make and use an invention, and thus whether a disclosure is enabling under 35 U.S.C. §112, ¶1, is a question of law that we review de novo, based on underlying factual inquiries that we review for clear error.").

The factual premises of the enablement analysis for biological processes were addressed in In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the court explaining that determination of whether the requisite amount of experimentation is undue may include consideration of:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id. at 737; 8 USPQ2d at 1404. See Amgen, Inc. v. Chugai Pharm. Co., 727 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (discussing application of the Wands factors). In In re Goodman, 11 F.3d 1046, 1052, 29 USPQ2d 2010, 2015 (Fed. Cir. 1993) the Wands factors were applied to a gene transformation method, the court finding that the method "would have required extensive experimentation that would preclude patentability." The disclosure in an assertedly anticipating reference must be adequate to enable possession of the desired subject matter. It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation. The principles underlying application of the criteria of enablement to the content of the prior art were discussed in In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985):

> It is well settled that prior art under 35 U.S.C. §102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it is not enabling. It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.

Id. at 533, 226 USPQ at 621. See also In re Borst, 345 F.2d 851, 855, 145 USPQ 554, 557 (CCPA 1962) ("the disclosure must be such as will give possession of the invention to the person of ordinary skill. Even the act of publication or the fiction of constructive reduction to practice will not suffice if the disclosure does not meet this standard.").

The determination of what level of experimentation is "undue," so as to render a disclosure non-enabling, is made from the viewpoint of persons experienced in the field of the invention. See Enzo Biochem, 188 F.3d at 1373-74 (discussing evidence of enablement and nonenablement in an unpredictable field of biotechnology). "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). In Wands the court observed that "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed . . . ." Id., quoting In re Jackson, 217 USPQ

804, 817 (Bd. App. 1982).

The Mullan reference contains an extensive description of the Swedish mutated gene, its source, the nature of the mutation, and its role in Alzheimer's disease. The reference also states that the invention provides a transgenic animal whose cells contain the mutated gene and express the Swedish mutated protein:

> The invention also provides a transgenic non-human animal containing, in a germ or somatic cell, the mutated nucleic acid of the invention, wherein the animal expresses a human amyloid precursor protein or fragment thereof which encodes an amino acid other than lysine at codon 670 and/or an amino acid other than methionine at codon 671.

Mullan, col. 4, lines 35-40. Elan argues that the Mullan reference does not show all of the limitations of the Elan claims and does not enable the transgenic animal it describes. Elan stresses the uncertainty and difficulty of producing a transgenic animal, and argues that although Mullan foresaw a transgenic mouse and presented a compilation of known methods of gene transfer, the reference does not teach or suggest which method might succeed in creating the desired mutated mouse. Mayo in turn stresses the comprehensiveness of the Mullan disclosure, and that Elan indeed eventually succeeded with one of the methods mentioned by Mullan, using the Swedish gene discovered by Mullan and a mouse species recited by Mullan.

The Mullan reference summarizes the various known gene transfer techniques, with citations to scientific literature describing these techniques. The following extract is illustrative:

> One approach to creating transgenic animals is to target a mutation to the desired gene by homologous recombination in an embryonic stem (ES) cell line in vitro followed by microinjection of the modified ES cell line into a host blastocyst and subsequent incubation in a foster mother (see Frohman and Martin, ~~Cell~~ (1989) 56:145). Alternatively, the technique of microinjection of the mutated gene, or a portion thereof, into a one-cell embryo followed by incubation in a foster mother can be used. Certain possibilities for the general use of transgenic animals, particularly transgenic animals that express a wild-type APP fragment, are disclosed in Wirak et al., the EMBO Journal, 10(2) 289-296 (1991); Schilling et al., ~~Gene~~ 98(2) 225-230 (1991); Quon, et al. (1991) Nature 352:239; Wirak, et al. (1991) Science 253:323; and Kawabata, et al. (1991) Nature 354:476. Alternatively, viral vectors, e.g., Adeno-associated virus, can be used to deliver the mutated gene to the stem cell. In addition, such viral vectors can be used to deliver the mutated gene to a developed animal and then used to screen (Mendelson et al., Virology 166:154-165; Wondisford et al. (1988) Molec. Endocrinol. 2:32-39 (1988)).

Mullan, col. 11, line 58 to col. 12, line 11. Mullan states that site-directed mutagenesis can also be used, preferably so as to produce the desired mutation. The Mullan reference also names various known cloning vectors for creation of transgenic animals, and states that the vector is "selected based on the size of the desired insert and the ability to produce stable chromosome integration." The Mullan reference contains additional information, with citations to scientific articles and textbooks, proposing how vectors "can be constructed," the transgene "can be injected," and like statements.

Elan stresses that Mullan does not suggest which, if any, of the methods and vectors he cites might reasonably be predicted to succeed in producing a mouse operatively harboring the Swedish mutation. As explained in Enzo Biochem, 188 F.3d at 1372, "an enablement determination is made retrospectively, i.e., by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time." Thus the enablement of the Mullan and Elan mice would be determined separately.

The issue is not whether the Mullan teachings are an accurate compilation of the state of the scientific art at that time, and they are not challenged on that ground. The issue is whether his teachings enabled a person of ordinary skill, without undue experimentation, to produce the desired transgenic mouse. The district court did not directly address the question of enablement, which was not the subject of the summary judgment motion.

Thus we remand for determination by the district court, upon consideration of relevant evidence and upon application of the law to the facts of this case, of whether the Mullan reference enabled persons of ordinary skill in the field of the invention to make the desired mutated mouse without undue experimentation.

II

This appeal was directed to the summary judgment that was granted on the ground of anticipation. Mayo's other defenses of invalidity, and the question of infringement, were not reached by the district court. Mayo's argument that the claims are invalid under §103 and/or §112, particularly if construed to have the breadth that Elan ascribes to them in order to reach the Mayo mouse, and any other issues properly raised, remain for consideration on remand.

REVERSED AND REMANDED

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[1] Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education & Research, 175 F. Supp.2d 1209 (N.D. Cal. 2000).

[2] A gene is a segment of DNA that encodes for and leads to the production, through several complex steps, of the sequence of amino acids that constitutes a protein. A mutation is a change in the gene DNA and the changes in the ensuing products. See Bruce Alberts et al., Essential Cell Biology (1998), Ch.6 "DNA," Ch.7 "From DNA to Protein."

[3] The positions at codons 670/671 (Mullan) and codons 596/597 (Elan) are the same, due to differing starting points in the APP chain. See '486 patent, col. 11, lines 29-34.