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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Defendant-Appellee.

DECIDED: August 30, 2002

Before NEWMAN, GAJARSA, and DYK, Circuit Judges.

Opinion for the court filed by Circuit Judge NEWMAN. Dissenting opinion filed by Circuit Judge DYK.

NEWMAN, Circuit Judge.

Elan Pharmaceuticals, Inc. and Athena Neurosciences, Inc. (collectively "Elan") appeal the decision of the United States District Court for the Northern District of California, granting summary judgment in favor of the Mayo Foundation for Medical

Education and Research ("Mayo").[1] The district court held that Elan's two patents in suit, United States Patent No. 5,612,486 for "Transgenic Animals Harboring APP Allele Having Swedish Mutation" (the '486 patent) and continuation Patent No. 5,850,003 for "Transgenic Rodents Harboring APP Allele Having Swedish Mutation" (the '003 patent), inventors Lisa McConlogue and Jun Zhao, are invalid on the ground of anticipation by United States Patent No. 5,455,169 for "Nucleic Acids for Diagnosing and Modeling Alzheimer's Disease" (the Mullan patent). We reverse the summary judgment, for the legal requirements of anticipation were not met on the facts of record, and remand for further proceedings.

BACKGROUND

Alzheimer's disease is a progressive neurodegenerative disease that primarily afflicts the elderly. Elan's '486 and '003 patents are directed to transgenic animals whose genetic makeup has been altered so that they are susceptible to Alzheimer's disease. The DNA of these animals has been modified to contain a mutated human gene called the

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

"Swedish mutation," for the gene was isolated from the cells of a Swedish family having an unusually high incidence of early-onset Alzheimer's disease.[2]

The brains of people with Alzheimer's disease contain abnormal tangles and deposits of plaques. At the time of these Elan inventions it was known that a principal component of these plaques is a protein fragment called beta-amyloid peptide (betaAP, also designated âAP and Aâ). The presence of betaAP in the brain is believed to induce or foster formation of the Alzheimer's plaques. It was known that betaAP may be formed when a protein produced in the brain, called the amyloid precursor protein (APP), is cleaved by enzymes in the brain. The Elan patents summarize scientific research in this field, including various reported mutations. Elan explains that an enzyme called beta-secretase cuts the APP molecule between amino acids 596 and 597, releasing a larger protein fragment called the amino terminal fragment (ATF-betaAPP); and an enzyme called gamma-secretase releases the smaller betaAP fragment from the remaining portion of the APP. This mechanism is illustrated in the Elan brief as follows:

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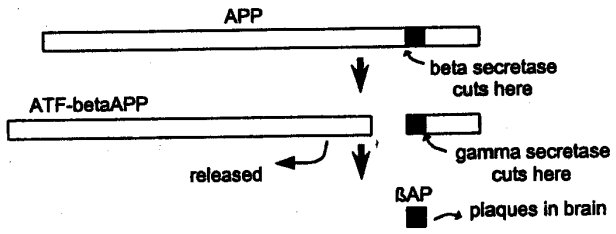
[2] A gene is a segment of DNA. A mutation is a change in a gene and the resulting change in a protein produced by the gene. A gene produces a protein by first copying (transcribing) a portion of DNA into an intermediate strand designated mRNA; the mRNA then produces, through several complex steps, the sequence of amino acids that constitutes the protein. This procedure is called "gene expression." See Bruce Alberts et al., Essential Cell Biology (1998), Ch.6 "DNA," Ch.7 "From DNA to Protein."

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



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

The Prior Art

The prior art on which the district court based its summary judgment of anticipation is the Mullan patent. Dr. Mullan had learned of the Swedish family susceptible to Alzheimer's disease, obtained samples of their DNA, isolated the relevant mutated gene, and identified the nature and location of the mutation in the gene as well as in the mutated protein (APP_{sw}) expressed by the gene. Mullan explained that in the Swedish mutation the DNA nucleotides that encode codons 670 and 671[3] replace lysine and methionine, the amino acids normally encoded at these positions, with asparagine and leucine. Mullan states that transgenic animals containing the mutated gene can be used in Alzheimer's disease (AD) research and therapy:

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

> 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.
>
> * * *
>
> The invention also provides a method of screening for an agent capable of treating AD. The method comprises contacting these transgenic animals or host cell lines with the agent and monitoring the expression, processing or deposition of amyloid precursor protein or fragments thereof.

Mullan, col. 4, lines 36-64. Mullan states that the mutated human gene can be used to create transgenic animals in various ways; for example:

> In yet a further use of the present invention, the mutated gene (i.e., a variant APP codon 670/1 gene) can be excised for use in the creation of transgenic animals containing the mutated gene. For example, an entire human variant APP codon 670/1 allele can be cloned and isolated, either in parts or as a whole, in a suitable cloning vector (e.g., 1Charon35, cosmid, retrovirus or yeast artificial chromosome). The vector is selected based on the size of the desired insert and the ability to produce stable chromosome integration.

Col. 11, lines 23-31. Mullan also states that the mutated gene can be transferred to a mouse that preferably will express the variant human APP:

> The human variant APP codon 670/1 gene, either in parts or in whole, can be transferred to a host non-human animal, such as a mouse. As a result of the transfer, the resultant transgenic non-human animal will express one or more variant APP codon 670/1 polypeptides. Preferably, a transgenic non-human animal of the invention will express one or more variant APP codon 670/1 polypeptides in a neuron-specific manner (Wirak et al. (1991) EMBO 10:289). This may be accomplished by transferring substantially the entire human APP gene (encoding a codon 670/1 mutant) including the 4.5 kilobase sequence that is adjacent to and upstream of the first major APP transcriptional start site.

Col. 11, lines 32-43. Mullan discusses the various known procedures of gene transfer, citing scientific articles as to each "approach" used to create transgenic animals:

> 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)).

Col. 11, line 58 to col. 12, line 11. Mullan also states that the mouse gene allele can be mutated to produce a mutation corresponding to the Swedish mutation:

> Site-directed mutagenesis and/or gene conversion can also be used to mutate a murine APP gene allele, either endogenous or transfected, such that the mutated allele does not encode lysine/methionine at the codon position in the mouse APP gene that corresponds to codon 670/1 (of APP770) of the human APP gene (such position is readily identified by homology matching of the murine APP gene or APP protein to the human APP gene or APP770 protein). Preferably, such a mutated murine allele would encode asparagine or leucine at the corresponding codon position.

Col. 12, lines 12-21.

It is undisputed that Mullan did not produce a transgenic animal with the Swedish mutation, or determine which of the known procedures would be effective for this purpose, or suggest conditions or details of any method for successful production of the desired animal. Expert witnesses for both sides testified as to the difficulty, uncertainty, unpredictability, and low success rate of each method that has been used to create transgenic animals.

The Elan Patents

The Elan patents describe the production and characteristics of transgenic rodents, specifically mice, whose DNA contains a gene harboring the Swedish mutation, which gene expresses human APP having the Swedish mutation. This APP_{sw} in turn produces human betaAP by action of the mouse enzymes. Expert witnesses for both sides testified as to the unpredictability of the process and the various steps thereof, for not all of the known methods may work, very few attempted gene transfers are successful, and of the relatively few mice that may accept the Swedish gene, not all will express the mutated human APP in a way that is subject to enzymatic cleavage to produce betaAP.

Elan explains that the production of betaAP in the mouse brain is difficult to detect because the betaAP molecule is relatively small. The Elan patents report detecting the betaAP by detecting the larger cleavage fragment, ATF-betaAPP. Claim 1 of the '486 patent includes this limitation:

> 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.

The '003 patent differs from the '486 patent in that the '003 claims include a promoter and a polyadenylation site. Claim 1 of the '003 patent follows:

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.

For both patents, dependent claims 2 and 3 add the limitations that the rodent is murine (mouse) and that the transgene is nonhomologously integrated. These limitations are not asserted to add patentable distinctions. Elan concentrates on the '486 patent on this appeal.

The Mullan patent was prior art based on its filing date, and the examiner granted the Elan patents only after Elan added the final clause to the claims. Elan argues on this appeal that its claims are limited by the presence of detectable ATF-betaAPP in the rodent brain, that this limitation is not shown by Mullan, and thus that as a matter of law the claims cannot be "anticipated." Elan states that “ATF-betaAPP was not even disclosed in humans until after Mullan was filed,” and thus that this limitation cannot be deemed "inherent" in the Mullan disclosure.

The district court found that although Mullan does not mention the formation of ATF-betaAPP, its formation is inherent in Mullan's general teachings of transgenic mice with the Swedish mutation. The court found that the Elan claims do not require that the claimed mice be tested for detectable ATF-betaAPP in brain homogenate. Thus the court found

that Mullan anticipates the Elan claims, and on summary judgment held the claims of both patents invalid on this ground.

DISCUSSION

The grant of summary judgment on a question of fact requires that "when the facts are viewed in the light most favorable to the non-moving party and all doubts are resolved in favor of the non-movant, there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 247-48 (1986). Elan argues that the factual and legal criteria of anticipation were not met. Elan also argues that summary judgment was inappropriate because material facts were in dispute, and that Elan would prevail if the disputed facts were resolved in its favor.

A

To be patented an invention must be new. 35 U.S.C. §§101, 102(a), (e). If it is not new, that is, if it was known to others, it is said to be "anticipated." Hoover Group, Inc. v. Custom Metalcraft, Inc., 66 F.3d 299, 302, 36 USPQ2d 1101, 1103 (Fed. Cir. 1995) ("lack of novelty (often called 'anticipation') requires that the same invention, including each element and limitation of the claims, was known or used by others before it was invented by the patentee"). Anticipation is a question of fact, as is the question of inherency. In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). Its proof differs from that for obviousness, 35 U.S.C. §103, in that prior knowledge by others requires that all of the elements and limitations of the claimed subject matter must be expressly or inherently described in a single prior art reference. In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999); Constant v. Advanced Micro-Devices, Inc., 848 F.2d 1560, 1571, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988). The single reference

must describe and enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. Crown Operations International, Ltd. v. Solutia Inc., 289 F.3d 1367, 1375, 62 USPQ2d 1917, 1921 (Fed. Cir. 2002); In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it").

The anticipating reference "must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." PPG Industries, Inc. v. Guardian Industries Corp., 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996). When anticipation is based on inherency of limitations not expressly disclosed in the assertedly anticipating reference, it must be shown that the undisclosed information was known to be present in the subject matter of the reference. Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991). An inherent limitation is one that is necessarily present; invalidation based on inherency is not established by "probabilities or possibilities." Scaltech, Inc. v. Retec/Tetra, LLC., 178 F.3d 1378, 1384, 51 USPQ2d 1055, 1059 (Fed. Cir. 1999).

B

The district court found that the Elan claims were anticipated by Mullan because use of the standard procedures set forth in Mullan would be expected to produce a statistically small percentage of transgenic mice, and some of these mice would be expected to produce detectable ATF-betaAPP on enzymatic cleavage. The court deemed it irrelevant

that the ATF-betaAPP was not described in the prior art. The court found that since the low success rate for gene transfer and expression was known, it was a matter of statistical probability that a few successful results would be obtained. Thus the district court found that the Elan invention was anticipated by Mullan.

Elan argues that Mullan does no more than teach broad known "recipes" for gene transfer, and that the Mullan disclosure is simply an invitation to experiment, with no assurance of success. That is clearly so. Although Mullan described known procedures for making a transgenic animal, he neither described every element of the claims, nor taught, in terms other than by trial and error and hope, production of a transgenic mouse having detectable ATF-betaAPP in brain homogenate. General instructions to conduct such failure-prone activities as gene transfer between humans and animals, and the ensuing uncertainties with respect to gene expression and enzymatic cleavage of the mutated human protein with animal enzymes, do not meet the legal criteria of “anticipation” of the successful product of transgenic activity. A general recitation of known procedures, none of which was carried out by Mullan, does not defeat the "novelty" of the specific mouse that was actually produced by Elan.[4]

Elan states that the concluding clause of its claims, the processing of the human APP_{sw} to form detectable ATF-betaAPP in the rodent brain, is the "key element" of the claims. Elan stresses that the patent examiner required the inclusion of this limitation in order to distinguish the Mullan reference, for Mullan does not mention producing detectable

[4] In support of its argument on the uncertainty and difficulty of producing a successful transgenic mouse using known general procedures, Elan points out that the accused Mayo mouse was the 2,576th mouse that was screened.

ATF-betaAPP or its use as a proxy for detecting the smaller betaAP molecule. Elan argues that detection of the ATF-betaAPP permits determination of when the Swedish DNA has been successfully transferred and the mutated gene is successfully operating to produce the desired mutated protein and the desired enzymatic cleavage.

Mayo does not dispute that the Mullan reference makes no mention of the formation of ATF-betaAPP in detectable amounts in brain homogenate. Mayo argues, and the district court found, that this claim limitation is "inherent" in Mullan because a successful transgenic procedure and ensuing enzymatic cleavage will produce ATF-betaAPP. However, this was not shown by Mullan, and there was no evidence that the formation and detection of ATF-betaAPP in the transgenic mouse brain with the Swedish mutation was known to persons of ordinary skill in the field of the invention. Inherency cannot be based on the knowledge of the inventor; facts asserted to be inherent in the prior art must be shown by evidence from the prior art. Cf. In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (criticizing the "hindsight syndrome wherein that which only the inventor taught is used against its teacher"). The purpose of the rule of inherency is to accommodate common knowledge, knowledge that judges might not know but that would be known to practitioners in the field. Finnigan Corp. v. Int'l Trade Comm'n, 180 F.3d 1354, 1365, 51 USPQ2d 1001, 1009 (Fed. Cir. 1999). On the law of anticipation, precedent has not improved on the words of Judge Learned Hand:

> No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. If the earlier disclosure offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation.

Dewey & Almy Chemical Co. v. Mimex Co., 124 F.2d 986, 989 (2d Cir. 1942).

We conclude that the legal requirements of anticipation were not met. The summary judgment of invalidity based on anticipation is reversed, and the case is remanded for further proceedings.

C

Mayo states that the Elan position on infringement is that the claims of the patents in suit cover all transgenic mice with the Swedish mutation, and that if the claims are construed as broadly as Elan proposes, they are invalid under §103 or §112. These issues were not decided by the district court; they are not before us for review.

D

We respond to the remarks of our colleague in dissent, for he has inaccurately perceived the "ground" on which our decision "rests." The ground of our decision is, simply, that a novel patented product is not "anticipated" if it did not previously exist.

The dissenter objects to what he calls the patenting of "existing inventions." We too object to the patenting of existing inventions. However, Elan is not patenting something that previously existed, for Elan's mouse did not exist. While Mullan surely had the concept of creating a transgenic mouse with the mutated Swedish gene, as we have illustrated *ante*, Mullan did not make such a mouse and he did not tell (or know) which, if any, of the standard procedures from the scientific literature might be effective in achieving the complex series of transformations needed for a successful product. A general proposal to make a product that has not been made does not meet the criteria of "anticipation." Indeed, Mayo affirms in its brief that no mice had been made by Mullan; Mayo also affirms, contrary to the statements of the dissent, that "Mayo admits that some of the mice made according to the recipe [in the Mullan patent] will not have detectable ATF." Mayo brief at 19.

The dissent proposes that this decision will "have serious and unfortunate consequences in the future by permitting the securing of patent rights to existing inventions

so long as the patent applicant identifies an inherent characteristic of that product that was not identified in the prior art," citing In re Cruciferous Sprout Litigation, 2002 U.S. App. LEXIS 17185 (Fed. Cir. 2002). We repeat, the Mullan mouse did not exist, quite unlike the broccoli sprouts of the Cruciferous Sprout Litigation, "long well known in nature and eaten by humans for decades." Id. at *5.

The dissenter appears to urge the unpatentability of any product that has been suggested but never made. This approach would eliminate even the possibility of patent protection for any transgenic product that may have been envisioned but not yet produced. A better rule is the established law, whereby new products are not "anticipated" when they did not previously exist, whether or not the process for making them is generally known. Although our colleague postulates "serious and unfortunate consequences in the future" if the Elan mouse is deemed patentable, others may believe that without the possibility of a patent on a new transgenic mouse, the hypothetical mouse envisioned by Mullan might well remain no more than a hypothesis. Determination of which consequence is fortunate or unfortunate is an important policy question; the law of anticipation as applied herein does not change existing policy.

"Anticipation" in the patent sense means that the subject matter was previously known. A precatory suggestion of general procedures that may or may not succeed in producing the novel product, a product that has not previously been produced, does not convert the suggested product into a previously existing product. The witnesses were in agreement that at the time the Mullan application was filed neither Mullan nor anyone else (1) had made a mouse harboring the Swedish mutated gene, (2) knew whether the mouse DNA would accept the Swedish gene, (3) knew if the mouse cell would then express the

human mutated protein of the Swedish family, or (4) knew whether the mouse enzymes would cleave the human mutated protein to produce human betaAP. Elan's expert Dr. Mobley stated, without disagreement, that "cells expressing the transgene have to correctly fold the protein, correctly modify it through glycosylation, correctly traffic it from internal to surface membranes, correctly traffic it through the endosomal pathway, and make it available to enzymes that modify it." Dr. Lieberburg, Elan's Chief Scientific and Medical Officer, stated that scientists were "at a great loss as to understand whether mice were even capable . . . of ever generating specific APP fragments that could be studied for drug discovery."

It is undisputed that Mullan had not made a mouse by any of his proposed procedures, and all of the scientists agreed that it cannot be predicted which, if any, procedure will ultimately succeed. General recipes of uncertain success do not convert a hoped-for product into one that previously existed. Our colleague in dissent states that despite Elan's statement that a successful mouse is a "tiny subset" of the transgenic mice that might be produced using Mullan's recipes, and despite the agreement of Mayo's witnesses with this scientific fact, the few successes that might be achieved (that is, that would possess the desired characteristics) form their own subset, thus placing the successful mouse in the prior art. That is not law of anticipation.

We observe the dissent's statement that an inventor's own disclosure can be used against him to prove anticipation. That statement is inaccurate. Patentability requires novelty and unobviousness in light of the prior art, not in light of what the inventor knew and included in his patent application. "Anticipation is the epitome of obviousness," Structural Rubber Products Co. v Park Rubber Co., 749 F.2d 707, 716. 223 USPQ 1264 1271 (Fed. Cir. 1984), and both are measured by what was previously known to persons in the field of the invention, as discussed in precedent. And as we have stated, the scope of the Elan claims was not decided, nor was it decided whether the Elan claims, upon correct construction, would cover the specific Mayo mouse. These issues are not before us on this appeal.

Finally, we note the dissent's observation that Elan's claims do not "require . . . a method of detection" of the ATF-beta APP. Elan has separate patents related to the method. See, e.g., U.S. Patent No. 5,441,870 (Method for monitoring cellular processing of â-amyloid precursor protein) to Seubert et al., claiming: "A method for monitoring cellular processing of â-amyloid precursor protein (â-APP) in cells, said method comprising detecting a soluble â-APP fragment secreted from said cells, and a substance which specifically binds to said soluble â-APP fragment, wherein the amino acid sequence of said â-APP fragment extends substantially from the amino-terminus of â-APP to the amino-terminus of â-amyloid peptide (â-AP)."

REVERSED AND REMANDED

United States Court of Appeals for the Federal Circuit

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Defendant-Appellee,

DYK, Circuit Judge, dissenting.

The majority decision in this case rests upon the ground that an inventor's own disclosure may not be used under 35 U.S.C. § 102 as proof of anticipation by inherent disclosure in a prior art reference. This decision contradicts our own case law, which holds that knowledge of an inherent characteristic in the prior art is irrelevant. As we recently recognized in In re Cruciferous Sprout Litigation, No. 02-1031, slip op. at 12 (Fed. Cir. Aug. 21, 2002), on the issue of inherency "[i]t matters not that those of ordinary skill heretofore may not have recognized these inherent characteristics." Here, as in Cruciferous, while Elan "may have recognized something quite interesting about those [mice], it simply has not invented anything new." Id. at 13. This decision, if followed, will have serious and unfortunate consequences in the future by permitting the securing of patent rights to existing inventions so long as the patent applicant identifies an inherent characteristic of that product that was not identified in the prior art. That has never been our law. I respectfully dissent.

I

The patents asserted herein are U.S. Patent Nos. 5,612,486 ("the '486 patent") and 5,850,003 ("the '003 patent") (collectively "the Elan patents"). The sole independent claim of the '486 patent recites in relevant part:

> A transgenic rodent . . . comprising a transgene encoding a heterologous APP polypeptide having the Swedish mutation . . . 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 mouse.

Claim 1 of the '486 patent (emphases added). The sole independent claim of the '003 patent recites in relevant part:

> A transgenic rodent . . . comprising a transgene comprising . . . a DNA segment encoding a heterologous APP polypeptide . . ., 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.

Claim 1 of the '003 patent (emphases added). Because these claims are directed to transgenic rodents, the methods by which they are produced are not elements of the claims. Nor is there any claim to a method for detecting ATF-betaAPP.

Despite the clear language of the claims mandating their interpretation as products (transgenic rodents), much effort both at the district court and here on appeal has been expended on arguments incorrectly interpreting the claims in terms of methods. Elan argues, for example, that U.S. Patent No. 5,455,169 to Mullan (hereinafter "Mullan"), cited by the Mayo Foundation for Medical Education and Research (hereinafter "Mayo") as anticipating the claims of the Elan patents, fails to teach "how to detect ATF-betaAPP, much less how to detect the fragment in a brain homogenate." (Appellants' Br. at 23.) The

claims of the Elan patents, however, require only detectable ATF-betaAPP and not a method of detection.

According to Elan, the '486 and '003 "patents required that its transgenic mice do all these things: [1] carry the APP_{SW} transgene, [2] express the APP_{SW} protein and [3] process the APP_{SW} to ATF-betaAPP such that the levels of ATF-betaAPP are detectable." (Appellants' Br. at 21.) As admitted by Elan in its brief on appeal, "Elan does not dispute that the specification of the Mullan patent disclosed a transgenic mouse harboring a human APP gene with the Swedish mutation." Id. at 17. In other words, the first element was disclosed. On appeal Elan also does not contend that the second element was not disclosed.[5] Elan contests solely the third aspect of the claims. Elan bases the novelty of its claimed rodents on the "critical element—processing APP to ATF-betaAPP in an amount sufficient to be detectable in a brain homogenate." Id. Mayo concedes that Mullan fails to expressly disclose this element of the claimed invention, but counters that this characteristic was inherent in the disclosure of Mullan. The only issue, therefore, is whether the rodent of Mullan will inherently produce ATF-betaAPP in a sufficient amount to be detectable in its brain homogenate.

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[5] The majority appears to suggest that this element was not disclosed in Mullan, but this issue was not raised on appeal. In any event, the Mullan patent discloses the second element, stating "[a]s a result of the transfer, the resultant transgenic non-human animal will express one or more variant APP codon 670/1 polypeptides." Mullan, col. 11, ll. 34-36. The majority cites no authority suggesting that any more detailed description was required. To be sure the Mullan reference must have been enabling in this respect, In re Donohue, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985), and there may be a question as to whether it was enabling. But Elan has deliberately decided not to mount an enablement challenge to the Mullan patent, apparently for the reasons explained by the district court relating to potential for such arguments to invalidate Elan's own claims for lack of enablement. Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research, 175 F. Supp. 2d 1209, 1212 (N.D. Cal. 2000).

II

On summary judgment the district court ruled that Mullan inherently anticipates the claims of the Elan patents, finding:

> The mice claimed in the patents-in-suit are merely a subset of the mice described in Mullan. Some of the mice made using the process disclosed in Mullan (which is essentially the same process disclosed in the patents-in-suit) would inevitably have detectable levels of ATF-betaAPP. Were Plaintiffs to contend otherwise, their own patents would not be enabled. Mullan therefore inherently includes the [detectable ATF-betaAPP] limitation of the final "wherein" clauses of the asserted claims.

Elan Pharms., Inc., 175 F. Supp. 2d at 1212.

The majority disagrees, apparently because no extrinsic evidence of inherency existed in the prior art. The majority states:

> there was no evidence that the formation and detection of ATF-betaAPP in the transgenic mouse brain with the Swedish mutation was known to persons of ordinary skill in the field of the invention. Inherency cannot be based on the knowledge of the inventor; facts asserted to be inherent in the prior art must be shown by evidence from the prior art. Cf. In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (criticizing the "hindsight syndrome wherein that which only the inventor taught is used against its teacher").

Ante at 11.

But this is not the correct analysis. This is not an obviousness case. The injunction in Dembiczak against using an inventor's own disclosure against him was in the context of a section 103 obviousness determination requiring "the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." 175 F.3d at 999, 50 USPQ2d at 1617 (citing W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)). The perceived problem with combining references using hindsight to render

a claimed invention obvious is that it "simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability." Id. This fear of hindsight recreation in the context of obviousness determinations, however, is not applicable in the context of inherency.

There is simply no basis in our law to support the proposition that the source of proof for inherency must be found in the prior art and cannot be found in a patentee's own disclosure or other source. In Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991), the court noted that "[t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence." Id. at 1268, 20 USPQ2d at 1749. Thus evidence extrinsic to the cited prior art reference may be used, i.e., the party raising the issue of inherency may fill in the gap in the disclosure using any source. The majority's contrary conclusion is incorrect as a matter of law, and directly contradicts our law, which has repeatedly recognized that the discovery of an inherent characteristic of an old product cannot be patented. Cruciferous, slip op. at 12; In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) ("When the claimed [inventions] are not novel they are not rendered patentable by recitation of properties, whether or not these properties are shown or suggested in the prior art." (emphasis added)); Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 782, 227 USPQ 773, 779 (Fed. Cir. 1985) ("[I]t is immaterial, on the issue of their novelty, what inherent properties the [disclosed products] have or whether these applicants discovered certain inherent properties").

III

Because the disclosures of the Elan patents may be used as proof that the Mullan transgenic rodent inherently possessed the claimed characteristic, the remaining question

is whether the Elan patents, in fact, provide that proof. They clearly do. The specification of the '003 patent teaches:

> Newly identified secreted fragments comprise amino-terminal portion of ßAPP (Aß) which remains after the cleavage and will be referred to hereinafter as the amino-terminal fragment form of ßAPP (ATF-ßAPP) [ATF-betaAPP]. ATF-ßAPP is believed to be the product of an alternative secretory processing pathway for Aß, which pathway is present even in normal (non-diseased) cells. It is further believed, however, that the alternate secretory pathway may be responsible for an essential event in the production of Aß in diseased cells in patients, and that abnormal production of AFT-ßAPP may be involved in diseases related to Aß plaque . . . .
>
> Particularly preferred animal models for ß-secretase cleavage of Aß are transgenic animals which express the Swedish mutation of the Aß gene . . . . <u>It has been found that such transgenic animals, particularly transgenic mice, produce high quantities of the AFT[sic ATF]-ßAPP</u> which may [be] detected according to the methods of the present invention. <u>In particular, it has been found that Swedish mutation of Aß produces quantities of the ATF-ßAPP which will usually be at least two-fold higher than wild type human ßAPP expressed in animals</u>.

'003 patent, col. 12, ll. 21-42 (emphases added). The "discoveries" discussed in the preceding passage are two-fold: first, that the ß-secretase cleavage (metabolism) of the Swedish mutation form of APP to produce the ß-amyloid peptide (ßA) results in a secondary "newly identified" fragment, ATF-ßAPP; and second, that the newly discovered fragment is found in "high quantities" in transgenic mice having the Swedish mutation form of APP.

As Elan concedes on appeal, "the specification of the Mullan patent disclosed a transgenic mouse harboring a human APP gene with the Swedish mutation." (Appellants' Br. at 17.) More than simply "harboring" the gene as suggested by Elan, however, Mullan discloses a transgenic mouse that will <u>express</u> the gene to produce the Swedish APP and then <u>metabolize</u> the APP to produce the ß-amyloid peptide for the study of the underlying biochemistry of that metabolism. Mullan, col. 11, ll. 5-36 ("[S]uch model systems provide a tool for defining the underlying biochemistry of APP and ß-amyloid metabolism . . . . The

human variant APP codon . . . can be transferred to a host non-human animal, such as a mouse. As a result of the transfer, the resultant transgenic non-human animal will express one or more variant APP codon 670/1 polypeptides."). As disclosed in the '003 specification, Swedish APP to ß-amyloid metabolism directly produces the "newly identified" ATF-ßAPP metabolite. '003 patent, col. 12, ll. 21-22. Further, transgenic mice that carry out the Swedish APP to ß-amyloid metabolism produce "high quantities" of the ATF-ßAPP metabolite. Id. at col. 12, ll. 35-42. Because the claims are not limited to a particular "method of detection," but rather broadly recite the requirement that the fragments be "detectable," a mouse that metabolizes APP to produce the ß-amyloid peptide in sufficient amounts to permit the study of the underlying biochemistry of that metabolism would necessarily produce detectable amounts of the ATF-ßAPP metabolite.

Elan argues that "[t]he transgenic mice claimed by Elan's patents are only a tiny, and at the time of Mullan unexpected, subset of the larger population of transgenic mice that might be produced by following the Mullan 'recipe.'" (Appellants' Reply Br. at 6.) In fact, the claimed mice are not a tiny subset of the mice disclosed in Mullan. To be sure, Mullan discloses a method for producing transgenic mice not all of which will successfully express the Swedish form APP. However, the Swedish form APP characteristic is disclosed in Mullan, and in each and every case of a mouse that processes Swedish form APP to produce the ß-amyloid chain as disclosed in the Mullan patent, that mouse will also produce ATF-ßAPP as claimed in the Elan patents. '003 patent, col. 12, ll. 21-42. Thus, the rule that "[i]nherency . . . may not be established by probabilities or possibilities," In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981) (citation omitted), is not violated by finding the claims of the Elan patent anticipated by a mouse according to

Mullan (expressing and metabolizing the Swedish form APP), which will always possess the ATF-ßAPP characteristic.

The district court correctly concluded that the claims of the Elan patents are invalid as inherently anticipated by Mullan.

For the foregoing reasons, I respectfully dissent.