Not Reported in F.Supp., 1998 WL 151411 (D.Del.)
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United States District Court, D. Delaware.
AJINOMOTO CO., INC., Plaintiff,
v.
ARCHER–DANIELS–MIDLAND CO., Defendant.

No. 95–218–SLR.
March 13, 1998.

Edward M. McNally, and Peter A. Pietra, of Morris, James, Hitchens & Williams, Wilmington, Delaware, of counsel Arthur I. Neustadt, Marc R. Labgold, William J. Healey, and Catherine B. Richardson, of Oblon, Spivak, McClelland, Maier & Neustadt, P.C., Arlington, VA, Thomas Field, and Lawrence Rosenthal, of Strook & Strook & Lavan, New York City, for plaintiff.

Jack B. Blumenfeld, and Thomas C. Grimm, of Morris, Nichols, Arsht & Tunnell, Wilmington, Delaware, of counsel Charles A. Laff, John T. Gabrielides, Kevin C. Trock, of Laff, Whitesel, Conte & Saret, Ltd., Chicago, Illinois, J. Alan Galbraith, and Ari S. Zymelman, of Williams & Connolly, Washington, D.C., for defendant.

OPINION

ROBINSON, J.

I. INTRODUCTION

***1** Plaintiff Ajinomoto Co., Inc. ("Ajinomoto") filed this suit pursuant to 35 U.S.C. § 271(g) against defendant Archer–Daniels–Midland Co. ("ADM") on April 6, 1995 seeking damages (lost royalty income) and an injunction against defendant Archer–Daniels–Midland ("ADM") for alleged infringement of a patent that is directed to a method for the preparation of bacterial strains possessing enhanced capability of producing amino acids.

Specifically, Ajinomoto charges that ADM willfully infringed claims 1 and 2 of U.S. Patent No. 4,278,765 ("the '765 patent") entitled "Method for Preparing Bacterial Strains Which Produce Amino Acids" issued on July 14, 1981. The priority patent to this patent was filed in the former Soviet Union on June 30, 1978.

Defendant denies infringement and challenges the validity and enforceability of the '765 patent under 35 U.S.C. §§ 112 ("obviousness"), 103 ("best mode" and "enablement"), and 115 and 116 ("oath of applicant"). Specifically, ADM charges that: (1) the specification of the '765 patent: (a) does not disclose the best mode contemplated by the inventors of carrying out their invention, (b) fails to enable the full scope of generic claims 1 and 2 without undue experimentation, and (c) lacks the deposit of the biological materials in a depository that will distribute samples of the material to members of the public who wish to practice the invention after the patent issues (§ 112); (2) the differences between the patented invention and the prior art are such that claims 1 and 2 would have been obvious to one of ordinary skill in the pertinent art (§ 103); and (3) not all of the inventors personally signed the declarations required to grant the '765 patent (§§ 115, 116). Additionally, ADM contends that Ajinomoto lacks standing to sue ADM for infringement of the '765 patent because the chain of title of the '765 patent from the named inventors to Ajinomoto was not established. Moreover, ADM affirmatively defends that the '765 patent is invalid because the patent applicants conducted themselves inequitably in their prosecution of the patent application by withholding and concealing prior art and by concealing the best mode of carrying out the invention.

The court has jurisdiction over this matter pursuant to 28 U.S.C. § 1338(a).

The parties tried this matter to the court from October 28, 1996 through November 11, 1996. The following constitutes the court's findings of fact and conclusions of law pursuant to Fed.R.Civ.P. 52(a).

II. FINDINGS OF FACT

A. The Invention

1. **Amino Acids.** The '765 patent is directed to a

method for the construction of genetically engineered bacterial strains possessing an enhanced capability of producing selected amino acids, such as threonine, without the need for additional growth factors. (Joint Exhibit ("JX") 1 at col. 3, lines 1–4) Amino acids are the building blocks of proteins. Proteins are complex macromolecules composed of long chains of amino acids that carry out structural and/or catalytic functions in cells. (D.I. 307 at 97–99) There are twenty amino acids: alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine, aspartic acid, glutamic acid, lysine, arginine, and histidine.

***2** 2. The '765 patent specifically discloses a method for producing an Escherichia coli ("E.coli") bacteria capable of overproducing the amino acid threonine. (JX 1) Threonine is of great industrial importance. It is an essential amino acid which, because it cannot be produced by any animal, must be supplied through dietary supplements. ADM's animal feed supplements supply various essential amino acids, including threonine.

3. A bacterial strain is a type or variety of a particular species of bacteria. There are thousands of known species of bacteria, as well as many bacterial strains within each species. All bacteria naturally make amino acids. Bacterial strains prepared in accordance with the patented technology can reduce the cost of producing amino acids, which are used, *inter alia*, as feedstuff and food additives in the agriculture and food industry. (JX 1 at col. 1, lines 8–12)

4. **Threonine Biosynthesis.** Threonine synthesis in a cell is a five step process. (Docket Item ("D.I.") 308 at 322–24; D.I. 313 at 941; Defendant's Exhibit ("DX") 298 at 346; DX 1005) In step 1, aspartate is converted into aspartyl phosphate. (D.I. 313 at 940–43; DX 298 at 346; DX 1005) Step 2 involves the conversion of aspartyl phosphate into aspartate semialdehyde. (D.I. 313 at 940–43; DX 298 at 346; DX 1005) The third step involves the conversion of aspartate semialdehyde into homoserine. (D.I. 313 at 940–43; DX 298 at 346; DX 1005) In step 4, homoserine is converted into O-phospho homoserine. (D.I. 313 at 940–43; DX 298 at 346; DX 1005) And finally, in step 5, O-phospho homoserine is converted into threonine. (D.I. 313 at 940–43; DX 298 at 346; DX 1005) Subsequently, some of the threonine is converted into isoleucine; the product of the *ilvA* gene catalyzes the first step in this transformation. (D.I. 313 at 940–43; DX 298 at 346; DX 1005) Through separate pathways, the process also results in the synthesis of lysine and methionine from the threonine precursors aspartate semialdehyde and homoserine, respectively. (D.I. 313 at 940–43; DX 298 at 346; DX 1005)

5. In E. coli[FN1] the entire process is catalyzed by a variety of enzymes,[FN2] three of which are coded by the threonine operon.[FN3] (D.I. 307 at 105–06; D.I. 313 at 947; DX 298 at 346; DX 1005) The threonine operon contains three structural genes: *thrA*, *thrB*, and *thrC*. (D.I. 307 at 105–06; D.I. 313 at 947; DX 298 at 346; DX 1005) The *thrA* gene codes for a bifunctional enzyme—aspartokinase for $thrA_1$ and homoserine dehydrogenase for $thrA_2$—which catalyze steps 1 and 3, respectively. (D.I. 307 at 105–06; D.I. 313 at 940–43; DX 298 at 346; DX 1005) The two remaining genes, *thrB* and *thrC*, code for homoserine kinase (step 4) and threonine synthetase (step 5), respectively. (D.I. 307 at 105–06; D.I. 313 at 940–43; DX 298 at 346; DX 1005)

FN1. The biosynthetic pathway for the production of threonine is not the same in all bacterial species. (D.I. 307 at 944–946) For example, with respect to *Corynebacteria*, although the basic steps in the pathway are the same, the number of isoenzymes involved in the various steps varies as does the method of regulation. (D.I. 313 at 944–46) In addition, in *Corynebacteria* although the *thrA* and *asd* genes are together on one part of the bacterial chromosome, the *thrB* and *thrC* are on two separate pieces of DNA. (D.I. 313 at 944–46)

FN2. The first step is catalyzed by three isoenzymes, the second by one, the third by two, the fourth by one, and the fifth by one. (D.I. 313 at 941) An isoenzyme (or isozyme) is one of a group of enzymes that are very similar

in catalytic properties, but can be distinguished based on variations in physical properties.

FN3. The term operon is defined as "[a] unit of genetic expression consisting of one or more related genes and the operator and promotor sequences that regulate their transcription." Albert L. Lehninger, *Principles of Biochemistry* 977 (Sally Anderson & June Fox eds., 1982). In the '765 patent, the term operon is defined as "a jointly controlled group of genes generally monitoring the synthesis of a single product, e.g. aminoacid." (JX 1 at col. 1, lines 49–51)

6. The product of the *asd* gene,[FN4] which is located outside of the threonine operon (approximately 1500 genes away), catalyzes the conversion of aspartyl phosphate into the semialdehyde of aspartic acid (the second step in threonine synthesis). (D.I. 313 at 947) This is not a limiting step in the biosynthetic process.

FN4. Although Ajinomoto asserts that testimony regarding the role of the *asd* gene in the biosynthesis of threonine should be discarded because of insufficient notice, the issue was raised by Ajinomoto's expert witness, Dr. Joseph O. Falkinham III, on cross-examination when he was questioned regarding threonine synthesis in E. coli.

***3** 7. In E. coli, regulation of the threonine operon is accomplished by means of a multivariant repression mechanism (negative feedback regulation), so that when a large amount of a particular product is formed, it blocks its own synthesis. (D.I. 313 at 942) With respect to the first step of threonine synthesis, lysine inhibits one of the isozymes, methionine inhibits a second isozyme, and isoleucine and threonine inhibit the third isozyme. (D.I. 313 at 940–43; DX 298 at 346; DX 1005) Lysine and methionine also regulate their own synthesis. (D.I. 313 at 940–43; DX 298 at 346; DX 1005) In addition, threonine and isoleucine inhibit one of the isozymes involved in step 3. (D.I. 313 at 940–43; DX 298 at 346; DX 1005) Besides the feedback inhibition effect that changes the activity of the level of the available enzyme, isoleucine and threonine also affect the level of available enzyme—as the levels of isoleucine and threonine increase, the amount of enzyme decreases. (D.I. 313 at 940–43)

8. **The Technology Developed by the Genetika Researchers.** The method of preparation set forth in the '765 patent was developed by fourteen researchers at the Institute for Genetic Engineering and Industrial Microbiology ("Genetika") in the former Soviet Union. (D.I. 307 at 123–24) In developing the process, the researchers combined skills from both classical genetics and recombinant DNA technology. (D.I. 307 at 126) Although not the first scientists to employ recombinant DNA technology, the Genetika researchers were the first in the former Soviet Union to do so. (DX 1100 at 30–31) Unlike their peers in other countries who were applying recombinant DNA technology[FN5] to the development of pharmaceuticals, the Genetika researchers applied this technology to the production of enzymes and, as in the case of the '765 patent, amino acids. (D.I. 307 at 124–26)

FN5. Herb Boyer and Stanley Cohen of Stanford University and the University of California, San Francisco respectively developed recombinant DNA technology. (D.I. 307 at 111) The technology was first described in a paper in The Proceedings of the National Academy of Sciences in November 1973. (D.I. 307 at 111) As compared to classical genetics, which typically involves exposing microorganisms to mutagens that randomly alter genetic material and then screening for mutants with desired characteristics, recombinant DNA technology involves the making of specific alterations in DNA, generally through the cutting and then ligating of DNA from different sources. (D.I. 307 at 111)

9. In order to create a bacterial strain capable of overproducing threonine, the Genetika researchers used a strain of E. coli that was feedback resistant for the amino acid threonine. (JX 1 at col. 3, lines 30–36) Using recombinant DNA technology,[FN6] the

researchers isolated the threonine operon from the strain and combined this chromosomal fragment with a plasmid. FN7 (JX 1 at col. 3, lines 30–36) This hybrid plasmid was then inserted into a host bacterial strain that was auxotrophic FN8 with respect to threonine and contained a partial block ("leaky auxotroph") in the related step of metabolism, the conversion of threonine to isoleucine. (JX 1 at col. 3, lines 46–51) The resultant strain of bacteria was capable of the over production of threonine.

FN6. For basic background information about molecular biology and recombinant DNA technology, see *In re O'Farrell,* 853 F.2d 894, 895–99 (Fed.Cir.1988).

FN7. The term plasmid refers to "[a]n extrachromosomal, independently replicating small circular DNA molecule." Albert L. Lehninger, *Principles of Biochemistry* 977 (Sally Anderson & June Fox eds., 1982).

FN8. An auxotrophic bacterial strain possesses a mutation that renders it "defective in the synthesis of a given biomolecule, which must thus be supplied for its normal growth." *Principles of Biochemistry* 970 (Sally Anderson & June Fox eds., 1982).

B. The '765 Patent Application

10. **The Russian Patent Application.** On June 30, 1978, fourteen Genetika researchers FN9 filed a Russian patent application entitled "Method for Preparing Strains Producing Aminoacids" (application no. 2639616) ("the Russian patent application"). (Plaintiff's Exhibit ("PX") 2) This patent was directed to "a method for preparing strains of microorganisms possessing an increased ability of producing aminoacids [sic] and lack of demands for additional growth factors." (PX 2 at 80) According to Soviet law, the Russian patent application was personally signed by all fourteen inventors. (D.I. 196 at Ex. 5, ¶ 44)

FN9. The fourteen inventors were: Vladimir G. Debabov, Jury I. Kozlov, Nelli I. Zhdanova, Evgeny M. Khurges, Nikolai K. Yankovsky, Mikhail N. Rozinov, Rustem S. Shakulov, Boris A. Rebentish, Vitaly A. Livshits, Mikhail M. Gusyatiner, Sergei V. Mashko, Vera N. Moshentseva, Ljudmila F. Kozyreva, and Raisa A. Arsatiants.

***4** The Russian patent application listed sixteen references, the pertinent contents of which were identified by use of reference numbers throughout the text of the specification. (PX 2 at 98) Of these references, only the following are relevant to the case at bar: (1) an article authored by several of the named co-inventors of the '765 patent (Gusyatiner, Zhdanova, Livshit [s]; and Shakulov) entitled *Investigation of the function of the relA gene in the expression of amino acid operons: Communication II. Influence of the allelic state of the relA gene on oversynthesis of threonine by a mutant of Escherichia coli K–12 resistant to beta-hydroxynorvaline* appearing in the publication Genetika 14(6) (June 1978) ("Genetika II") and (2) an article entitled *A Suitable Method for Construction and Molecular Cloning Hybrid Plasmids Containing EcoRI-fragments of E. coli Genome* authored by Kozlov et al. (including the named co-inventors Kozlov, Rebentish, and Debabov) published in Molecular and General Genetics in 1977 ("the Kozlov article").

11. **U.S. Patent Application.** The same fourteen inventors who filed the Russian patent application filed the United States counterpart to the Russian patent application on June 28, 1979, two days before the end of the one year priority period. FN10 (PX 2) The inventors claimed a priority filing date of June 30, 1978 based upon the Russian application. (PX 2) The following documents were included along with the U.S. patent application: (1) a Russian Language Declaration for Original Patent Application ("Russian Language Declaration"); (2) the original Russian patent application; and (3) an English translation of the Russian patent application. (PX 2)

FN10. Title 35 U.S.C. § 119 provides a right of priority for U.S. patent applications if an application for a patent on the same invention was previously filed in a foreign country. Section 119 provides, in part:

> An application for patent for an invention filed in this country ... shall have the same effect as the same application would have if filed in this country on the date on which the application for patent ... was first filed in such foreign country, **if the application in this country is filed within twelve months** from the earliest date on which such foreign application was filed; but **no patent shall be granted on any application for patent for an invention which had been patented ... in any country more than one year** before the date of the actual filing of the application in this country....
>
> 35 U.S.C. § 119 (emphasis added).

12. **The Inventors' Signatures.** The Russian Language Declaration and the Russian patent application contain fourteen signatures purporting to be the signatures of the fourteen original inventors. (PX 2 at 48–53) With respect to the Russian Language Declaration, each signature is followed by a typed date of June 21, 1979. (PX 2 at 48–53) Dr. Juri Ivanovich Kozlov FN11 testified that the signature on the Russian Language Declaration is not his own; however, the signor, who he believed to be an employee in Genetika's patent department, "had [his] permission to put [his] signature in [his] absence." (DX 1106 at 144) Dr. Kozlov further testified that he did not remember if he read the declaration or whether it was explained to him before he granted permission for someone to sign it for him. (DX 1106 at 145–46)

> FN11. Only two of the original fourteen inventors were deposed in this litigation. None of the inventors testified at trial.

13. Dr. Vladimir Georgievich Debabov testified that his signature on the Russian Language Declaration is, in fact, his own. (DX 1100 at 42) Although he does not remember the date on which he signed the declaration, he believed it must have been June 21, 1979 since that is the date on the form. (DX 1100 at 42)

14. **The Prior Art References.** The U.S. patent application omitted the sixteen references found in the Russian patent application. However, unlike the Russian patent application, the U.S. patent application cited six publications which described in detail the method of *in vitro* preparation of hybrid DNA molecules and the introduction of these molecules into a recipient strain by means of transformation or transfection using a plasmid or bacteriophage as a vector. (JX 1 at col. 2, lines 37–44) Of these publications two are relevant to the case at bar: (1) an article authored by Clarke and Carbon entitled *Biochemical Construction and Selection of Hybrid Plasmids Containing Specific Segments of the Escherichia coli Genome*, which was published in Proc. Nat'l Acad. Sci. USA, Vol. 72, No. 11 in November 1975 ("the Clarke/Carbon article") and (2) the Kozlov article. (JX 1 at col. 2, lines 52–53, 56–58)

***5** 15. At the time the '765 patent application was submitted, applicants were encouraged to file a prior art statement listing therein, "in the opinion of the person filing[,] ... the closest prior art of which that person is aware." 37 C.F.R. § 1.97(a)–(b) (1978). Said statement was "not to be construed as a representation that a search ha[d] been made or that no better art exist[ed]." 37 C.F.R. § 1.37(b). The statement was to be accompanied by a copy of each listed patent or publication. 37 C.F.R. § 1.98(a). A prior art statement was not submitted as part of the '765 patent application.

According to ADM's expert in Patent and Trademark Office ("PTO") procedure, Mr. Van Horn, at the time of the invention, a PTO Examiner was not likely to review publications that were merely mentioned in the patent application. (D.I. 316 at 1420) Moreover, he testified that unless circumstances arose that necessitated an Examiner to review a priority patent application (e.g., a challenge to the priority date), the content of a priority patent was not reviewed as part of a normal examination of a patent application. (D .I. 316 at 1427–28; DX 268 at 28) If an applicant wanted to be assured that the Examiner considered certain information, he could submit copies of publications or other information to the PTO. (D.I. 316 at 1421) Mr. Van Horn also testified that there were two ways for an Examiner to indicate that a particular reference had

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