ATTACHMENT A

FOCUS - 1 of 1 DOCUMENT

AMGEN, INC. Plaintiff, v. CHUGAI PHARMACEUTICAL CO., LTD., AND GENETICS INSTITUTE, INC., Defendants

Civ. Action No. 87-2617-Y

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS

1989 U.S. Dist. LEXIS 16110; 13 U.S.P.Q.2D (BNA) 1737

December 11, 1989, Decided; As Amended January 30, 1990

PRIOR HISTORY: *Amgen, Inc. v. Chugai Pharm. Co., LTD., 1989 U.S. Dist. LEXIS 19148* (D. Mass., May 26, 1989)

OPINION BY: [*1]

SARIS, Magistrate

OPINION:

MEMORANDUM AND ORDER

PATTI B. SARIS, UNITED STATES MAGISTRATE

I. INTRODUCTION

This action is about the highly competitive race between two leading biotechnology companies, among others, to clone the gene for the human hormone erythropoietin ("EPO"). A glycoprotein which stimulates red blood cell production, EPO is useful in one treatment of anemia, especially chronic anemia associated with end stage renal disease.

Plaintiff Amgen, Inc. ("Amgen"), a biotechnology company located in Thousand Oaks, California, was the first to clone the gene in October, 1983, when inventor Dr. Fu-Kuen Lin obtained the amino acid sequence for EPO and designed two sets of probes to isolate the EPO gene from a "genomic library," a mixture containing most, if not all, of the human genes. Amgen filed an application for a patent on December 13, 1983 in the United States Patent and Trademark Office ("PTO"). After rejections by the various patent examiners of the claims in three prior applications, U.S. Patent No. *4,703,008* (the " 008 patent"), entitled "DNA Sequences Encoding Erythropoietin," was issued on October 27, 1987. The patent claims genetic materials and genetically [*2] engineered host cells useful in the recombinant production of erythropoietin.

Defendant Genetics Institute, Inc. ("GI"), a biotechnology company located in Cambridge, Massachusetts, was the second to clone the gene. Dr. Edward Fritsch, using a similar technique to Dr. Lin's, isolated the gene in July, 1984, and on January 3, 1985, GI filed its 258 patent application with the PTO. GI does not contest that Dr. Lin was the first actually to clone the gene, but, among other things, argues that Dr. Fritsch invented the methodology necessary to clone the gene in December, 1981 before Dr. Lin conceived of it and that by 1983 Dr. Lin's methodology was obvious. On May 9, 1989, the PTO declared an "interference" between the 258 application and the 008 patent.

GI is also the owner of U. S. patent No. *4,677,195* (the " 195 patent"), entitled "Method for the Purification of Erythropoietin and Erythropoietin Compositions," which was issued on June 30, 1987. The patent application was filed on January 11, 1985. Defendant Chugai pharmaceutical Co., Ltd. ("Chugai"), a company located in Tokyo, Japan, is the exclusive licensee of this patent. Inventor Dr. Rodney M. Hewick claims as his invention, [*3] among other things, "homogeneous erythropoietin" which has certain weight and biological activity characteristics, and which rises as a single peak on reverse phase high performance liquid chromatography. On January 31, 1989, Judge William Young issued a Memorandum and Order granting partial summary judgment in favor of GI and Chugai on the claim that Amgen's EPO, manufactured through recombinant methods, literally infringed the 195 patent. However, Judge Young did not rule on the validity of that patent. See *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 706 F. Supp. 94 (D. Mass. 1989)* ("Amgen").

This is how Dr. Lin isolated the EPO gene and pulled it out of the genomic library. (Tr. 5, 55). Dr. Lin believed that his cloning method was different from what people had done before, and was a scientific advance, because he used big 128-sequence complex mixtures of probes to screen a genomic library which is a more complex library than one made up of cDNA. (Tr. 5, 56, 59). He also believed that the use of 128 probes was a larger number than others had used to screen a genomic library. (Tr. 5, 95).

The successful cloning of the EPO gene took place in September or early October, 1983. (Tr. 4, 64-66; 5, 123-124). This was the first time that Lin ever designed, ordered and used two sets of probes, both fully degenerate, from two different regions of the EPO gene to screen a genomic library. (Tr. 5, 91, 124). Amgen (someone other than Dr. Lin) sequenced the gene to confirm it was the EPO gene. (Tr. 4, 74).

In late October, 1983, Lin cloned the monkey cDNA EPO sequence. (Tr. 4, 72). On December 3, 1983, Lin also hybridized the human EPO gene to monkey Epa cDNA so that he could determine from an electron micrograph which area of the human DNA consisted of introns, and what the sizes [*44] of the exons and introns were. (Tr. 4, 68-72; PX 63-38).

Lin filed his first patent application on December 13, 1983. (Tr. 4, 74). Amgen issued a press release at about the same time. (Tr. 4, 76; PX 49). Amgen's successful cloning of the gene was reported in McGraw-Hill's Biotechnology Newswatch, dated January 2, 1984. (Tr. 4, 77).

By January 10, 1984, Amgen had expressed human EPO in human embryonic kidney cells called "293" cells and in COS cells, which are monkey kidney cells. (Tr. 4, 75-77; PX 63-39; PX 63-41). Someone other than Dr. Lin did the work with the mammalian expression system. (Tr. 5, 51-52). Lin was personally involved in the E. Coli expression of EPO. (Tr. 5, 52). On February 13 and 14, 1984, Amgen conducted experiments to show that the recombinant human EPO produced in the COS cell was biologically active. (Tr. 4, 80).

On February 21, 1984, Lin filed his second patent application. (Tr. 4, 81).

From March 1-9, 1984, Amgen conducted an in vivo bioassay and determined that the recombinant EPO was biologically active. (Tr. 4, 82-83).

On March 15, 1984, Lin obtained the human full length EPO cDNA gene. (Tr. 4, 83; 5, 28).

On April 5, 1984, Lin specified [*45] the nucleotides necessary to synthesize a human EPO gene which could be used for expression in yeast cells. (Tr. 4, 84-85). When a gene is synthesized by chemical means, the introns are excluded, and it is easier to manipulate the gene for expression in different organisms. (Tr. 4, 85).

By May 2, 1984, human rEPO had been expressed in CHO cells. (Tr. 4, 86). Jeff Browne and Ralph Smalling worked together on the EPO project team, which Lin continued to head through 1984, to develop a cell line in 1984. (Tr. 6, 66). In developing a cell line to express rEPO, Amgen used as starting material a mammalian host cell called CHO DHFR- (DuXB11) for transfection. (Tr. 6, 49; PX 2, Col. 26, 1. 51). This host cell was from a cell line developed by Professor Lawrence Chasin at Columbia University who has no connection with Amgen. (Tr. 6, 49). After transfection, Amgen had a heterogeneous cell population, and used MTX amplification and limited dilution cloning to develop a production cell line. (Tr. 6, 55-56). A heterogeneous cell population is called a cell strain, and a homogeneous population developed from one single cell is called a cell line. (Tr. 6, 65, 74). A master cell bank is created [*46] from the cell line. (Tr. 6, 75). A cell strain cannot be used for production purposes, only a cell line. (Tr. 6, 98).

By August 27, 1984, five different sublines of human EPO-CHO ("huEPO-CHO") had been produced. (Tr. 6, 66; DX 336). Browne had chosen two of the lines, B11 30/50/100 and B11 50 for a radioimmunoassay. (DX 336). Joan Egrie reported to Lin in September, 1984 that she had studied the huEPO-CHO cell line B11 30/50/100 for Epa production. (Tr. 6, 70). She also conducted a radioimmunoassay ("RIA") and in vivo assay of the produced EPO. (DX 337). At that point, Amgen had narrowed its consideration of cell strains to the B11 30/50/100 host cell. (Tr. 6, 71). On September 19, 1984, Dr. Browne told Lin that amplification of huEPO-CHO cells with MTX was continuing, and he was "getting ready to create a master cell bank from cell line B11 30/50/100." (Tr. 6, 73; DX 295). The cell strain B11 30/50/100 was the CHO B11 cell transformed with the human EPO gene and amplified through 30 nanomolar, 50 nanomolar and 100 nanomolar MTX. (Tr. 6, 93, 96; 10, 12). Nanomolar is a concentration measurement. (Tr. 6, 96). This strain was equivalent to B11 3,.1, which is a short-hand ray of [*47] describing the amplification process from 30 nanomolar MTX amplification through 100 nanomolar MTX amplification. (Tr. 6, 99; 10, 12).

By October 19, 1984, Dr. Browne had written a memorandum to Kirin-Amgen which identified Amgen's "current process for the production of EPO" from the "production cell line, CHO B11 3,.1." (DX 347). On October 31, 1984, Amgen decided that it would start making a master cell bank on November 26, 1984. (Tr. 6, 84; DX 291). By September, 1984, Amgen had decided that the best way to express EPO was from mammalian cells, not yeast cells or E. Coli bacterial cells. (Tr. 6, 83, 106).