Amgen Inc. v. F. Hoffmann-LaRoche LTD et al Doc. 485 Att. 21

EXHIBIT 15

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LA ROCHE LTD., a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN-LA ROCHE INC., a New Jersey Corporation, Defendants.	)	Civil Action No.: 05-12237 WGY

SUPPLEMENTAL EXPERT REPORT OF HARVEY F. LODISH, Ph.D.

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Goto *et al.* report that baby hamster kidney cell-produced EPO retains the carboxy-terminal arginine 166.[17] Given the impossibility in deducing the cleavage site, the difficulty in experimentally detecting the carboxy terminal cleavage, and given the variability in cleavage between cells, in my opinion Dr. Lin's specification was as precise as the subject matter permitted at the time with respect to the amino acid sequence of human EPO.

26. As to Dr. Flavell's discussion of the amino acid sequences described in Example 12 of the patent, which concerns expression of human erythropoietin in *E. coli*, I believe that these examples support the Court's interpretation of "human erythropoietin." Example 12 demonstrates that the specification intended the term "human erythropoietin" to allow for additional structure, even in the form of an amino acid (Lin Example 12 at the amino terminus).

27. Dr. Flavell contends that I wrongly characterized Example 12 as producing a -1 to 166 protein in my Infringement Expert Report.[18] Dr. Flavell is correct that the Lin's *E. Coli* host cell example in the specification shows that a terminal methionine, and in some instances the initial alanine, were cleaved off after *E. coli* synthesis.[19] My point is not that human EPO recovered from the *E. coli* cells in Examples 11-12 must have a methionine attached. Rather, my point is that the specification explicitly includes polypeptides that have an additional methionine residue in its description of "human EPO." For example, the specification states: "Polypeptides

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processing of an arginine residue, and in some cases includes up to 15% of an EPO with 166 amino acids"); R001572151.

[17] Goto *et al*., "Production of Recombinant Human Erythropoietin in Mammalian Cells: Host Cell Dependency of the Biological Activity of the Cloned Glycoprotein" Biotechnology 6:67-71 (1988).

[18] Flavell Supplemental Report ¶¶ 17-18.

[19] '933 Patent, Col. 32:18-25.

of the invention may also include an initial methionine amino acid residue (at position -1)."[20] In addition, the specification describes Figures 10-15 and 7 as illustrating the "design and assembly of a manufactured gene encoding a ***human EPO translation product*** lacking any leader or presequence but including an initial ***methionine residue at position -1***."[21] A polypeptide containing methionine at position -1 was made by the *E. coli* cells in Examples 11-12, and the specification describes that polypeptide as "human EPO translation product" and "polypeptides of the invention" because, in my opinion, the polypeptide backbone of the protein produced by *E. coli.* in this Example contained the human EPO amino acids sequence. The fact that the methionine at position -1 was subsequently cleaved off in the cells after initial synthesis of the polypeptide, does not change this fact. Thus, in my opinion, one of ordinary skill in the art reading the specification in 1984 would have understood Lin's definition of "human EPO" did not exclude the presence of additional molecules attached to the amino acid sequence of human EPO such as a methionine. Such a polypeptide was still human EPO.

28. In summary, with Dr. Lin's specification in hand, one of ordinary skill in the art as of 1983 or 1984 would not have been at a loss to understand what "human EPO" was. The specification is rich with information, teachings and resources that provided for the first time structural information about what "human EPO" is and for the first time put the public in possession both of this powerful information and the actual claimed human EPO protein itself. In my opinion, Dr. Lin's claims were as precise as the subject matter permitted as of 1984, and were sufficiently clear, when read in light of the entire specification, to allow one skilled in the art to know what was claimed and what was not claimed.

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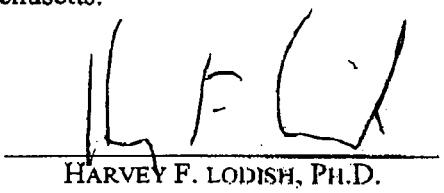
[20] '933 Patent, Col. 10:28-33.

[21] *Id*. at Col. 29:27-30.

Executed this 4th day of June, 2007 at Boston, Massachusetts.



HARVEY F. LODISH, PH.D.