The JOHNS HOPKINS UNIVERSITY, a Maryland Corporation, Baxter Healthcare Corporation, a Delaware Corporation, and Becton Dickinson and Company, a New
Jersey Corporation, Plaintiffs,
v.
CELLPRO, a Delaware Corporation, Defendant.

Civil Action No. 94-105-RRM.

United States District Court, D. Delaware.

June 28, 1996.

Holder of four patents relating to antibodies and purified suspensions of stem cells sued alleged infringer. Alleged infringer counterclaimed, asserting that patents were invalid and not infringed. Following jury verdict in favor of alleged infringer, patentee renewed motion for judgment as a matter of law or new trial. The District Court, McKelvie, J., held that: (1) two patents were infringed as a matter of law; (2) one patent was not invalid for lack of enablement as a matter of law; (3) patentee was entitled to new trial on issue of infringement of two other patents; (4) patentee was entitled to new trial on issue of obviousness of all patents; and (5) patentee was entitled to new trial on enablement of three patents.

Motion for judgment as a matter of law granted in part; motion for new trial granted in part.

[1] FEDERAL CIVIL PROCEDURE ⇐ 2608.1
170Ak2608.1
In deciding whether to grant judgment as a matter of law on particular issue after jury has returned verdict, court must determine whether substantial evidence exists in record to support jury's verdict when correct legal standard is applied; "substantial evidence" is quantum of evidence that reasonable jurors would accept as adequate to support finding under review.

See publication Words and Phrases for other judicial constructions and definitions.

[2] FEDERAL CIVIL PROCEDURE ⇐ 2609
170Ak2609
In deciding whether to grant judgment as a matter of law on particular issue after jury has returned verdict, court must consider all evidence and draw all reasonable inferences from evidence in light most favorable to nonmovant.

[3] FEDERAL CIVIL PROCEDURE ⇐ 2609
170Ak2609
In deciding whether to grant judgment as a matter of law on particular issue after jury has returned verdict, court may not determine credibility of witnesses, and it may not substitute its choice for that of jury as between conflicting elements of evidence.

[4] FEDERAL CIVIL PROCEDURE ⇐ 2334
170Ak2334
In deciding whether to grant new trial, court may consider, among other things, whether verdict is against weight of evidence, whether verdict turned on erroneously admitted evidence, or whether court improperly instructed jury.

[4] FEDERAL CIVIL PROCEDURE ⇐ 2336
170Ak2336
In deciding whether to grant new trial, court may consider, among other things, whether verdict is against weight of evidence, whether verdict turned on erroneously admitted evidence, or whether court improperly instructed jury.

[4] FEDERAL CIVIL PROCEDURE ⇐ 2339
170Ak2339
In deciding whether to grant new trial, court may consider, among other things, whether verdict is against weight of evidence, whether verdict turned on erroneously admitted evidence, or whether court improperly instructed jury.

[5] FEDERAL CIVIL PROCEDURE ⇐ 2339
170Ak2339
For purposes of motion for new trial, in determining whether verdict is against weight of evidence, court should not substitute its view of facts for that of jurors.

[6] FEDERAL CIVIL PROCEDURE ⇐ 2311
170Ak2311
Court may grant new trial even when judgment as a matter of law is inappropriate.

[7] FEDERAL CIVIL PROCEDURE ⇐ 2313
170Ak2313
Grant of new trial is within sound discretion of trial court.

[8] PATENTS ⇐ 323.3
291k323.3
To determine whether patent holder is entitled to judgment as a matter of law or new trial on issue of whether accused device infringes patent, court must first construe claims of patent and must then compare properly construed claims of patent to accused device to determine if all limitations in claims are present in device itself or in use of device.

[9] PATENTS ⇐ 314(5)
291k314(5)
Construction of patent claims is a matter for court.

[10] PATENTS ⇐ 165(3)
291k165(3)
In construing words and phrases in patent claim, court should give those words and phrases their ordinary meaning, unless specification clearly indicates that inventor intended different meaning.

[10] PATENTS ⇐ 167(1.1)
291k167(1.1)
In construing words and phrases in patent claim, court should give those words and phrases their ordinary meaning, unless specification clearly indicates that inventor intended different meaning.

[11] PATENTS ⇐ 159
291k159
In construing words and phrases in patent claim, court may consider other words in claim, other claims in patent, specification, prosecution history, expert testimony, and other extrinsic evidence.

[11] PATENTS ⇐ 165(2)
291k165(2)
In construing words and phrases in patent claim, court may consider other words in claim, other claims in patent, specification, prosecution history, expert testimony, and other extrinsic evidence.

[11] PATENTS ⇐ 165(5)
291k165(5)
In construing words and phrases in patent claim, court may consider other words in claim, other claims in patent, specification, prosecution history, expert testimony, and other extrinsic evidence.

[11] PATENTS ⇐ 167(1.1)
291k167(1.1)
In construing words and phrases in patent claim, court may consider other words in claim, other claims in patent, specification, prosecution history, expert testimony, and other extrinsic evidence.

[11] PATENTS ⇐ 168(2.1)
291k168(2.1)
In construing words and phrases in patent claim, court may consider other words in claim, other claims in patent, specification, prosecution history, expert testimony, and other extrinsic evidence.

[12] PATENTS ⇐ 101(2)
291k101(2)
Claim 1 of patent for all monoclonal antibodies that specifically bind to antigen identified as "CD34" claimed any monoclonal antibody that binds only to CD34 antigen through antigen-antibody interaction.

[13] PATENTS ⇐ 323.3
291k323.3
Holder of patent for all monoclonal antibodies that specifically bind to antigen identified as

"CD34" was entitled to new trial after jury found that patent had not been infringed; trial court had improperly construed patent at trial, great weight of evidence was in favor of infringement, and holder had not had adequate opportunity to cross-examine alleged infringer's expert.

[14] PATENTS ⇐ 101(2)
291k101(2)
In patent directed to purified suspension of stems cells, patent directed to method of creating such purified suspension of stem cells using "CD34" antibodies, and patent directed to method of using that purified suspension of stem cells in bone marrow transplants, phrase "substantially free" of mature lymphoid and myeloid cells required cell suspension that contained no more than 10% mature lymphoid and myeloid cells.

See publication Words and Phrases for other judicial constructions and definitions.

[15] PATENTS ⇐ 101(2)
291k101(2)
Step (b) of claim 1 of patent directed to method of creating purified suspension of stem cells using "CD34" antibodies meant contacting said cell suspension with any monoclonal antibody that binds only to "CD34" antigen through antigen-antibody interaction.

[16] PATENTS ⇐ 312(3.1)
291k312(3.1)
Patentee need not have tested accused device to prove patent infringement.

[17] PATENTS ⇐ 249.1
291k249.1
Use of monoclonal antibody known as "12.8" in devices for purifying stem cells infringed patent directed to purified suspension of stem cells.

[18] PATENTS ⇐ 249.1
291k249.1
Manufacturer of monoclonal antibody known as "12.8" induced infringement of patents directed to purified suspension of stem cells and method of using that purified suspension of stem cells in bone marrow transplants; numerous documents authored by manufacturer encouraged users of accused devices to use antibody to create suspension of purified stem cells.

[18] PATENTS ⇐ 259(1)
291k259(1)
Manufacturer of monoclonal antibody known as "12.8" induced infringement of patents directed to purified suspension of stem cells and method of using that purified suspension of stem cells in bone marrow transplants; numerous documents authored by manufacturer encouraged users of accused devices to use antibody to create suspension of purified stem cells.

[19] PATENTS ⇐ 323.3
291k323.3
Holder of patent directed to method of creating purified suspension of stem cells using "CD34" antibodies was entitled to new trial after jury found that patent had not been infringed; trial court had improperly construed patent at trial, great weight of evidence was in favor of infringement, and holder had not had adequate opportunity to cross-examine alleged infringer's expert.

[20] PATENTS ⇐ 16(2)
291k16(2)
Facts to consider when determining whether patent was obvious include scope and content of prior art, level of ordinary skill in art, differences between subject matter claimed and prior art, and other objective indicia of nonobviousness. 35 U.S.C.A. § 103.

[20] PATENTS ⇐ 16(3)
291k16(3)
Facts to consider when determining whether patent was obvious include scope and content of prior art, level of ordinary skill in art, differences between subject matter claimed and prior art, and other objective indicia of nonobviousness. 35 U.S.C.A. § 103.

[21] PATENTS ⇐ 312(4)
291k312(4)
Alleged infringer has burden of proving obviousness of patent by clear and convincing evidence. 35 U.S.C.A. § 103.

[22] PATENTS ⇐ 314(5)
291k314(5)
Ultimate determination of obviousness of patent is a question of law. 35 U.S.C.A. § 103.

[23] PATENTS ⇐ 323.3
291k323.3
Holder of patents directed to monoclonal antibodies to "CD34" antigen, to purified suspension of stem cells, to method of creating such purified suspension of stem cells using "CD34" antibodies, and to method of using that purified suspension of stem cells in bone marrow transplants, was entitled to new trial on issue of obviousness after jury found that patents were obvious; alleged infringer argued obviousness to jury based on prior art that was not properly identified in pretrial order and based on testimony that was not offered and admitted as relevant to issues directed to obviousness, and great weight of evidence suggested that alleged infringer had not met its burden of proving facts underlying obviousness. 35 U.S.C.A. § 103.

[24] PATENTS ⇐ 99
291k99
If specification requires one skilled in art to perform undue experimentation to practice invention claimed in patent, patent is invalid as not enabled. 35 U.S.C.A. § 112.

[25] PATENTS ⇐ 99
291k99
For purposes of enablement requirement of patent validity, determination of what constitutes undue experimentation requires application of standard of reasonableness, having due regard for nature of invention and state of art. 35 U.S.C.A. § 112.

[26] PATENTS ⇐ 99
291k99
Factors to consider in determining whether patent has been enabled are amount of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of invention, state of prior art, relative skill of those in art, predictability or unpredictability of art, and breadth of claims. 35 U.S.C.A. § 112.

[27] PATENTS ⇐ 312(4)
291k312(4)
Alleged infringer has burden of proving by clear and convincing evidence that patent has not been enabled. 35 U.S.C.A. § 112.

[28] PATENTS ⇐ 314(5)
291k314(5)
Ultimate question of whether specification enables invention claimed in patent is a question of law. 35 U.S.C.A. § 112.

[29] PATENTS ⇐ 323.3
291k323.3
Holder of patent that claimed all monoclonal antibodies that specifically bind to antigen identified as "CD34" was entitled to new trial on issue of enablement after jury found that patent was invalid as not enabled; it was not clear from evidence that alleged infringer had proven that patent was not enabled. 35 U.S.C.A. § 112.

[30] PATENTS ⇐ 99
291k99
Determination of enablement of patent depends upon specific facts of each case. 35 U.S.C.A. § 112.

[31] PATENTS ⇐ 99
291k99
Patent enablement requirement is met if description enables any mode of making and using claimed invention. 35 U.S.C.A. § 112.

[32] PATENTS ⇐ 99
291k99
Patent directed to purified suspension of stem cells was not invalid for lack of enablement. 35 U.S.C.A. § 112.

[33] PATENTS ⇐ 99
291k99
Patent specification need only enable one mode of making claimed invention. 35 U.S.C.A. § 112.

[34] PATENTS ⇐ 323.3
291k323.3
Holder of patent directed to method of creating purified suspension of stem cells using "CD34" antibodies was entitled to new

trial on issue of enablement after jury found that patent was invalid as not enabled; it was not clear from evidence that alleged infringer had proven that patent was not enabled. 35 U.S.C.A. § 112.

[35] PATENTS ⇐ 323.3
291k323.3
Holder of patent directed to method of using purified suspension of stem cells in bone marrow transplants was entitled to new trial on issue of enablement after jury found that patent was invalid as not enabled; it was not clear from evidence that alleged infringer had proven that patent was not enabled. 35 U.S.C.A. § 112.

[36] PATENTS ⇐ 99
291k99
Nothing in patent law requires that patentee must disclose data on how to mass produce invented process for patent to be enabled. 35 U.S.C.A. § 112.

[37] PATENTS ⇐ 99
291k99
Fact that others have developed commercial embodiments of claimed invention is irrelevant to determining issue of enablement of patent. 35 U.S.C.A. § 112.

PATENTS ⇐ 328(2)
291k328(2)
4,965,204, 5,035,994. Cited.

PATENTS ⇐ 328(2)
291k328(2)
4,965,680, 5,130,144. Infringed.

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OPINION

McKELVIE, District Judge.

This is a patent case. Plaintiff The Johns Hopkins University ("Hopkins") owns U.S. Patent No. 4,965,204 (the " '204 patent"). Hopkins has licensed the '204 patent to plaintiffs Baxter Healthcare Corporation ("Baxter") and Becton Dickinson and Company ("Becton Dickinson"). The '204 patent claims all monoclonal antibodies that specifically bind to the antigen identified as "CD34." On March 8, 1994, plaintiffs filed a complaint alleging that defendant CellPro, Inc. ("CellPro") is willfully infringing claims 1, 2, 4, and 5 of the '204 patent.

CellPro denied infringement and asserted certain affirmative defenses, including that the '204 patent is invalid and unenforceable. In addition, CellPro counterclaimed for plaintiffs' alleged violation of antitrust law and for a declaratory judgment that the '204 patent and three other patents owned by Hopkins, U.S. Patent Nos. 4,965,680 (the " '680 patent"), 5,035,994 (the " '994 patent"), and 5,130,144 (the " '144 patent"), are invalid, unenforceable, and not infringed. All four patents-in-suit are collectively known as the "Civin patents" after their inventor, Dr. Curt Civin. Civin is a physician and professor at *307 The Johns Hopkins University School of Medicine and The Johns Hopkins University Hospital in Baltimore, Maryland.

In their answer to CellPro's counterclaim, plaintiffs denied the invalidity and unenforceability of the Civin patents. In addition, they alleged that CellPro is infringing, contributorily infringing, and inducing infringement of the '680, '994, and '144 patents. Pursuant to a stipulation by the parties, the court issued an order deferring the antitrust phase of the case until after the patent issues were tried.

The case was tried to a jury beginning on July 24, 1995, on the issues of the infringement, validity, and enforceability of the Civin patents. During the trial, CellPro sought to introduce evidence on two invalidity

defenses, indefiniteness and inoperability, that it did not identify in the pre-trial order. The court requires parties to identify their specific contentions, and the evidence in support of those contentions, in the pre-trial in order to give the opposing party sufficient notice of those contentions before trial. Therefore, the court precluded CellPro from presenting evidence in support of indefiniteness or inoperability and from arguing these issues to the jury.

After the presentation of evidence, the court endeavored to construe the disputed claims of the Civin patents in accordance with Markman v. Westview Instruments, Inc., 52 F.3d 967, 979-81 (Fed.Cir.1995), aff'd, --- U.S. ---, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). See Johns Hopkins University v. CellPro, 894 F.Supp. 819, 826-29 (D.Del.1995) (setting out the court's construction of the claims). The court then instructed the jury on its construction of the claims and on the issues of law raised by the parties, except for the issues of infringement under the doctrine of equivalents and the enforceability of the Civin patents. Id. at 828-40 (setting out the final jury instructions). Shortly after the trial, the Court of Appeals for the Federal Circuit held that infringement under the doctrine of equivalents is an issue of fact for the jury. Hilton Davis Chemical Co. v. Warner-Jenkinson Co., 62 F.3d 1512 (Fed.Cir.1995).

On August 4, 1995, the jury returned a verdict in which it found that the claims of all of the Civin patents were invalid as obvious in light of the prior art. The jury also found that, except with respect to unasserted claims 3 and 6 of the '204 patent, each claim of the Civin patents was invalid as not enabled. The jury further found that CellPro did not literally infringe the claims of the '204 patent and that CellPro did not literally infringe, contributorily infringe, or induce infringement of the asserted claims of the '680, '994, and '144 patents.

On October 3, 1995, plaintiffs renewed a motion made during trial for judgment as a matter of law pursuant to Rule 50 of the Federal Rules of Civil Procedure ("FRCP"). Plaintiffs' motion seeks to establish the following: 1) that CellPro infringes the claims of the Civin patents literally and under the doctrine of equivalents; 2) that CellPro failed to prove by clear and convincing evidence that the claims of the Civin patents are obvious; and 3) that CellPro failed to prove by clear and convincing evidence that the claims of the Civin patents are not enabled. In the alternative, plaintiffs renewed a motion made during trial for a new trial pursuant to FRCP 59.

On April 24, 1996, the court heard oral argument on a number of post-trial motions filed by the parties, including plaintiffs' motion for judgment as a matter of law or, in the alternative, for a new trial. This is the court's decision on plaintiffs' motion for judgement as a matter of law or for a new trial.

I. FACTUAL AND PROCEDURAL BACKGROUND

In order to understand and construe the claims of the Civin patents, it is necessary to examine the physiology underlying the inventions claimed in the patents. First, the court will explain the basic physiology of blood. Second, the court will discuss the specific physiology underlying the Civin patents and the goals, methods, and results of Civin's research. Third, the court will recite the relevant claims of the '204, '680, '994, and '144 patents and discuss the construction given to those claims during the trial. Fourth, *308 the court will discuss CellPro's accused processes and products. The court draws the following facts from the testimony and exhibits offered at trial.

A. What is the Basic Physiology of Blood?

Blood consists of a number of components. There is a liquid, known as plasma, that makes the blood fluid and that contains certain proteins for clotting. In addition, there are a number of types of cells, known as red cells, platelets, and white cells, which are also called leukocytes. Red cells carry oxygen in the blood, whereas platelets cause blood

clotting. White cells are important for fighting infections and are part of the immune system.

White cells are divided into two large families, known as lymphocytes and granulocytes. There are different types of lymphocytes, such as T lymphocytes or T cells and B lymphocytes or B cells. T cells govern certain immune responses and are the ones that are destroyed by the AIDS virus. B cells make antibodies, which are important for certain kinds of responses to infections. There are also different types of granulocytes, such as neutrophils, eosinophils, and basophils. Neutrophils kill bacteria, whereas eosinophils and basophils respond to certain kinds of immune stimuli that are less well known.

Blood cells have a fairly short lifespan, and thus the body must produce millions of blood cells each day. Blood cells are manufactured in a tissue known as marrow in the cavity of some bones. In bone marrow, there exist cells known as a pluripotent stem cells that produce all types of blood cells. These stem cells, which are called pluripotent or multipotent because of the number of types of cells they can create, are very rare and difficult to locate. A stem cell produces other cells by dividing over and over until thousands of cells have been manufactured. This process of producing blood cells is called hematopoiesis.

At this stage, the stem cells are immature because they have not determined what type of cell they will become. A stem cell may become a lymphoid stem cell that can later become a B or T cell. Alternatively, a stem cell can become a myeloid stem cell that can later become a red cell, a platelet, or a granulocyte. Over time, these stem cells become progressively more differentiated, which is the word used to describe blood cell maturation. Lymphoid and myeloid stem cells differentiate into progenitor cells, which are uncommon but not as rare as stem cells. Progenitor cells still retain some ability to reproduce cells. For simplicity, the court will refer to both progenitor cells and stem cells as stem cells.

B. What Were the Goals, Methods, and Results of Civin's Research?

In the early 1980s, scientists were seeking ways of identifying and isolating blood cells in order to learn about diseases related to these cells. These scientists, including Civin, focused on the use of antibodies to label cells. As discussed above, antibodies respond to infections in the body. For example, if a bacteria is present, the body will produce an antibody that will bind to one side of the bacteria. To be more specific, the antibody binds to a site on the bacteria known as an antigen, which is a mass of protein and sugar on the cell. Since antigens often are larger than antibodies, antibodies sometimes connect with only a portion of the antigen, known as an epitope. Blood cells, including stem cells, have antigens as well. Thus, antibodies also can bind to blood cells that have the appropriate antigen.

There are different types of antibodies, such as IgG and IgM monoclonal antibodies. These types of antibodies have different characteristics, for example, IgM antibodies have 10 binding sites, whereas IgG antibodies have only 2 binding sites. All monoclonal antibodies have antigen-specific binding sites, however, meaning that the antibody will bind to only one type of antigen. There are a number of words that describe the interaction between an antibody and an antigen, such as binding, recognizing, adhering, detecting, marking, labeling, and selecting. Whatever word is used, however, the important fact is that the interaction is specific--one monoclonal antibody interacts with one antigen. Note, however, that many antigens *309 can bind to multiple antibodies, particularly because of the existence of multiple epitopes on those antigens.

Once an antibody attaches to an antigen on a cell, that cell is effectively flagged and scientists can use known techniques to separate the flagged cell from other cells. One such technique is called fluorescence-activated coating separation ("FACS") and involves coating the antibody with a colored dye. All the cells in the coated sample then are passed

through a machine that uses a laser to identify and separate the cells based on their color. Another separation technique that exists is called panning. Panning involves taking a standard laboratory dish called a petri dish, which is generally made of plastic, and placing the cells and the antibodies in the dish. The antibodies adhere to the cells with the appropriate antigen and they also adhere to the plastic, thereby attaching the cells to the petri dish. The remaining cells without the antigen float free. Afterwards, the free cells are gently washed away and the attached cells are recovered.

Civin was searching for an antigen that only would be found on stem cells. With this knowledge he could create antibodies to that antigen in order to identify and separate stem cells from other types of blood cells. One advantage that Civin sought by isolating stem cells relates to the treatment for leukemia. A common treatment for leukemia is radiation therapy, but bone marrow is sensitive to radiation and often becomes damaged. To replace damaged bone marrow, patients need bone marrow transplants. This bone marrow can come from another individual or from the recipient if recovered before the radiation therapy. Unfortunately, both sources pose a health risk to the patient. Using bone marrow from another individual can result in Graft Versus Host Disease ("GVHD"), in which the blood cells produced by the transplanted marrow attack the patient's body. Using bone marrow from the patient, however, can cause any cancerous cells in the removed marrow to be placed back in the body. Civin sought a method of isolating stem cells in order to create a purified, cancer-free suspension of such cells for use in bone marrow transplants.

Civin used the method developed by two scientists named Kohler and Milstein to discover the antigen for which he was looking. The Kohler/Milstein method involves first immunizing a mouse with a human cell, which makes the mouse capable of producing the relevant antibody. The mouse's B cells, the ones that produce antibodies, are then removed and chemically fused with an immortal cancer cell line from a mouse. The fused cells, called hybridomas, will have the combined qualities of a B cell and the cancer cell line--they will be immortal and they will have the ability to make one antibody. The hybridomas are then screened to discover an antibody that has the characteristic being sought, in this case one that binds to an antigen on stem cells but not on mature cells.

Civin was aware of a human immortal cancer cell line, known as KG-1a for its developers Drs. Koeffler and Golde, that had similar characteristics to very immature cells. He hypothesized that there might be an antigen on this immortal cell line that is also found on nonmalignant, immature human blood cells but not on mature human cells. He repeatedly immunized BALB/cJ female mice with the KG-1a cell line in accordance with the Kohler/Milstein method. He then fused SP-2 plasmacytoma cells with splenocytes, a type of antibody-producing B cell harvested from the immunized mice. Finally, he screened the hybridomas to discover antibodies that reacted to the immature KG-1a cell line but not mature granulocytes from a panel of human donors. Civin discovered one such antibody, suggesting that an antigen did exist only on immature cells. Civin named the antigen My-10. He called the antibody the anti-My-10 antibody, which is often shortened to the My-10 antibody.

Other scientists subsequently produced antibodies that bound to the antigen identified by Civin as My-10. These scientists participated in International Leukocyte Workshops in which they sought to exchange information and name various antibodies and antigens that had been produced. They set up clusters, which included all antibodies that labeled the same antigen or set of cells. Civin's My-10 antibody was the first of its kind because it was stage-specific--it was detectable *310 on immature cells but not on mature cells--and it was not lineage-dependent--it was found on many different types of immature cells. The My-10 antigen was given the designation "CD34" because it was the 34th cluster designation of an antigen. Thus, the My-10 antibody is called a CD34 antibody.

C. What are the Relevant Claims of the Civin Patents?

All four of the Civin patents arose from a single application filed on February 6, 1984. The patents share the same specification, but minor clerical differences between the patents have altered the column and line numbers. Therefore, any citations to the specification will refer to the '204 patent.

Each patent is directed to a different field of endeavor. The '204 patent is directed to monoclonal antibodies to the CD34 antigen. The '680 patent is directed to a purified suspension of stem cells. The '994 patent is directed to a method of creating such a purified suspension of stem cells using CD34 antibodies. Finally, the '144 patent is directed to a method of using that purified suspension of stem cells in bone marrow transplants.

1. The '204 patent

As issued, claim 1 states:

1. A monoclonal antibody which specifically binds to an antigen on non-malignant, immature human marrow cells, wherein said antigen is stage specific and not lineage dependent, and said antigen is also specifically bound by the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483;

(a) which antigen is present on non-malignant, human blood or bone marrow:

(i) colony-forming cells for granulocytes and monocytes (CFC-GM)

(ii) colony-forming cells for erythrocytes (BFU-E)

(iii) colony-forming cells for eosinophils (CFC-Eo)

(iv) multipotent colony-forming cells (CFC-GEMM), and immature lymphoid precursor cells;

(b) which antigen is present on a maximum of about 5% non-malignant, human marrow cells and a maximum of about 1% non-malignant, human peripheral blood cells; and

(c) which antigen is not present on non-malignant mature human myeloid and lymphoid cells.

Plaintiffs have argued, and it appears from the prosecution history, that the portion of claim 1 starting after "HB-8483" was incorrectly kept in the claims as the result of a typographical error. In addition, all of this information appears in the specification of the patent. Therefore, the court concluded at the pre-trial conference that claim 1 should read as follows:

1. A monoclonal antibody which specifically binds to an antigen on non-malignant, immature human marrow cells, wherein said antigen is stage specific and not lineage dependent, and said antigen is also specifically bound by the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483.

In their post-trial briefing, plaintiffs do not mention claim 2 and related claim 5 that they asserted at trial. Therefore, these claims are not relevant to this decision.

The reference in claim 1 to ATCC Accession No. HB-8483 relates to the American Type Culture Collection, which is a depository of biological specimens. Scientists can obtain samples of deposited cell lines to reproduce experiments performed by others. In this case, Civin deposited the hybridoma he created that produces the My-10 antibody. The specification details the experiments Civin performed to discover the CD34 antigen and to create hybridomas that produce the My-10 antibody to the CD34 antigen.

A trial, the parties disputed the meaning of the following terms in claim 1: 1) "specifically binds" and "specifically bound;" 2) "stage specific;" and 3) "wherein said antigen is stage specific and not lineage dependent, and said antigen is also specifically bound by the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483." The court found that phrases 1 and 3 could be read with their ordinary meaning and thus needed no additional explanatory language. *311 Johns Hopkins, 894 F.Supp. at 827-28. The court construed the term "stage specific" to mean "the antigen is on immature human marrow cells and not on mature human marrow cells." Id. at 827.

2. The '680, '994, and '144 patents

Claim 1 of the '680 patent states:
1. A suspension of human cells comprising pluripotent lympho-hematopoietic stems cells substantially free of mature lymphoid and myeloid cells.

Claim 5 of the '680 patent states:
5. A suspension of human cells from marrow or blood comprising cells having a cell-surface antigen recognized by the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483 and substantially free of cells that do not have a cell-surface antigen recognized by said antibody, said suspension having the ability to restore the production of lymphoid and hematopoietic cells to a human lacking said production.

Claim 1 of the '994 patent states:
1. A method of isolating a population of human cells containing pluripotent lympho-hematopoietic stem cells comprising:
(a) providing a cell suspension from human tissue, said tissue selected from the group consisting of marrow and blood;
(b) contacting said cell suspension with a monoclonal antibody to immature human marrow cells that is stage-specific and not lineage dependent so that said antibody binds to said stem cells, wherein said antibody specifically binds an antigen on human pluripotent lympho-hematopoietic stem cells said stem cells expressing an antigen that is specifically bound by the monoclonal antibody produced by the hybridomas deposited under ATCC Accession No. HB-8483 and does not specifically bind an antigen on mature, human myeloid and lymphoid cells; and
(c) separating and recovering from said cell suspension the cells bound by said antibody, said bound cells being substantially free of mature lymphoid and myeloid cells.

Claim 1 of the '144 patent states:
1. A method of transplanting stem cells comprising:
(a) providing a suspension of human cells comprising pluripotent lympho-hematopoietic stem cells substantially free of mature lymphoid and myeloid cells, having the ability to restore the production of lymphoid and hematopoietic cells in a patient where such production is lacking; and
(b) administering said cell suspension to a human patient in an amount effective to effect such restoration.

The language of the remaining claims of these patents is irrelevant to this decision.

At trial, the parties disputed the following language in each of the claims of the '680, '994, and '144 patents: "substantially free of mature lymphoid and myeloid cells." In addition, the parties disputed the following language in the '144 patent: 1) "administering said cell suspension;" and 2) "an amount effective to effect such restoration." The court found that these phrases could be read with their ordinary meaning and thus needed no additional explanatory language. Johns Hopkins, 894 F.Supp. at 827-28.

D. What are CellPro's Accused Processes and Products?

The Fred Hutchinson Cancer Research Center (the "Center") produced a monoclonal antibody, which it called 12.8, using substantially the same method that Civin used to produce the My-10 antibody. It published a paper in 1986 citing Civin's earlier work as a model and describing the characteristics of the 12.8 antibody. The authors of the article, Andrews, Singer, and Bernstein, stated that 12.8 had the same characteristics as My-10 in that it reacted with stem cells and not mature cells. They concluded that the antigens bound by 12.8 and My-10 might be the same.

Another scientist at the Center, Dr. Berenson, later discovered that 12.8 reacted with an antigen that was only on immature cells and that weighed 115 kilodaltons ("KD"), the *312 same weight as Civin's My-10 antigen. He concluded that the antigens were the same and thus 12.8 was a CD34 antibody.

At the Fourth and Fifth International Leukocyte Workshops on the use of antibodies, scientists confirmed that 12.8 and My-10 both specifically bind to the CD34 antigen. These scientists also discovered additional antibodies to the CD34 antigen, and they discovered that the CD34 antigen has at least three classes of epitopes to which these antibodies bind. Through testing, they determined that 12.8 and My-10 both bind to Class 1 Epitopes.

Berenson and others at the Center formed CellPro to develop commercial methods of using 12.8 to purify stems cells for laboratory and clinical use. The Center granted a license to CellPro to use the 12.8 antibody. Scientists at CellPro were interested in whether they could discover an advantage in using the 12.8 antibody over the My-10 antibody based on the differences between the two. Unlike My-10, 12.8 binds to primate cells, which allows scientists to use 12.8 in clinical trials with nonhumans. In addition, 12.8 can bind to biotin, which is a type of vitamin, whereas My-10 cannot. CellPro ultimately developed a new separation technology based in part on these advantages of the 12.8 antibody.

CellPro's process for purifying stem cells works as follows. CellPro adds blood cells to some of the 12.8 antibody that has been previously bound to biotin. These cells are poured into a column, inside of which are beads covered with avidin. Avidin binds tightly with biotin, locking the CD34 positive cells onto the walls of the column while the other CD34 negative cells are washed away. The column is then agitated to loosen the CD34 positive cells to obtain a purified suspension of stem cells. The entire process is known as Continuous Flow Immunoadsorption Technique, and the binding between avidin and biotin is called Avidin/Biotin Immunoaffinity.

CellPro manufactures two devices to perform this process, the Ceprate LC and the Ceprate SC. The Ceprate LC is smaller and is used for research applications. The Ceprate SC is larger to support clinical applications of the stem cell purification process, particularly for bone marrow transplants. Plaintiffs argue that CellPro's use of the 12.8 antibody in its Ceprate LC and SC machines (the "accused devices") infringes many of the claims of the Civin patents. They also argue that the Civin patents were nonobvious to one of skill in the art and that the specification enables all of the patents. Therefore, they argue that the jury's findings to the contrary are incorrect as a matter of law or, alternatively, that they are entitled to a new trial on these issues.

II. DISCUSSION

[1][2][3] In deciding whether to grant judgment as a matter of law on a particular issue after a jury has returned a verdict, the court must determine whether substantial evidence exists in the record to support the jury's verdict when the correct legal standard is applied. Markman v. Westview Instruments, Inc., 52 F.3d 967, 975 (Fed.Cir.1995), aff'd, --- U.S. ----, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). Substantial evidence is the quantum of evidence that reasonable jurors would accept as adequate to support the finding under review. Perkin-Elmer Corp. v. Computervision Corp., 732 F.2d 888, 893 (Fed.Cir.), cert. denied, 469 U.S. 857, 105 S.Ct. 187, 83 L.Ed.2d 120 (1984). The court must consider all evidence and draw all reasonable inferences from the evidence in the light most favorable to the nonmovant. Id. In addition, the court may not determine the credibility of the witnesses, and it may not "substitute its choice for that of the jury as between conflicting elements of the evidence." Id.

[4][5][6][7] In deciding whether to grant a new trial, the court may consider, among other things, whether the verdict is against the weight of the evidence, Wagner v. Fair Acres Geriatric Center, 49 F.3d 1002, 1017 (3d Cir.1995), whether the verdict turned on erroneously admitted evidence, Blanche Road Corporation v. Bensalem Township, 57 F.3d 253 (3d Cir.), cert. denied, --- U.S. ----, 116 S.Ct. 303, 133 L.Ed.2d 208 (1995), or whether the court improperly instructed the jury. Cooper Distributing Co. v. Amana Refrigeration, 63 F.3d 262 (3d Cir.1995); see generally *313 Lind v. Schenley Industries,

Inc., 278 F.2d 79, 90 (3d Cir.), cert. denied, 364 U.S. 835, 81 S.Ct. 58, 5 L.Ed.2d 60 (1960). In determining whether a verdict is against the weight of the evidence, the court should not substitute its view of the facts for that of the jurors. Wagner, 49 F.3d at 1017. Nevertheless, the court may grant a new trial even when judgment as a matter of law is inappropriate. Id. Ultimately, the grant of a new trial is within the sound discretion of the district court. Id.

A. Did the Jury Properly Find That CellPro Has Not Infringed Any of the Civin Patents?

[8] To determine whether plaintiffs are entitled to judgment as a matter of law or a new trial on the issue of whether CellPro's accused devices infringe the Civin patents, the court must undertake a two-step inquiry. The court first must construe the claims of the patent. Texas Instruments Inc. v. United States Int'l Trade Comm'n, 988 F.2d 1165, 1171 (Fed.Cir.1993). The court then must compare the properly construed claims of the patent to the accused devices to determine if all of the limitations in the claims are present in the devices themselves or in the use of the devices. Id.; Johnston v. IVAC Corp., 885 F.2d 1574, 1577 (Fed.Cir.1989).

[9][10][11] The construction of patent claims is a matter for the court. Markman, 52 F.3d at 979-81. In construing the words and phrases in a claim, the court should give those words and phrases their ordinary meaning, unless the specification clearly indicates that the inventor intended a different meaning. Intellicall, Inc. v. Phonometrics, Inc., 952 F.2d 1384, 1388 (Fed.Cir.1992). The court may also consider other words in the claim, other claims in the patent, the specification, the prosecution history, and expert testimony and other extrinsic evidence. Markman, 52 F.3d at 979-81; Elf Atochem North America, Inc. v. Libbey-Owens-Ford Co., 894 F.Supp. 844, 859 (D.Del.1995).

1. Has CellPro infringed claim 1 of the '204 patent?

Plaintiffs contend that no evidence exists in the record to support the jury's finding of noninfringement with respect to claim 1 of the '204 patent when that claim is properly construed. CellPro argues that plaintiffs failed to meet their burden of proving infringement of claim 1. Plaintiffs' argument requires the court to revisit the topic of claim construction with respect to claim 1 because the court's construction of this claim at trial appears to have been in error.

a. What is the proper construction of claim 1?

[12] Plaintiffs' noninfringement argument largely derives from its proposed construction of claim 1. Plaintiffs argue that the phrase "wherein said antigen is stage specific and not lineage dependent, and said antigen is also specifically bound by the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483" (the " 'wherein' clause") refers to the antigen now identified as CD34. In addition, they argue that the phrase "specifically binds" refers to the chemical interaction between an antigen and an antibody. Thus, plaintiffs propose the following construction of claim 1--any monoclonal antibody that binds to the CD34 antigen through an antibody-antigen interaction. CellPro argues that plaintiffs' claim construction impermissibly seeks to rewrite claim 1 by avoiding specific limitations of the claims. CellPro apparently does not contest the court's previous construction of these claims.

1) What is the meaning of the "wherein" clause?

Plaintiffs' proposed claim construction of the "wherein" clause is highly unorthodox in that it seeks to define a large number of words in the claim with reference to a single alphanumeric reference, CD34. The basis for this unorthodox construction, however, appears to derive from the difficulty of describing the antigen to which the '204 patent refers. As Justice Burton observed in Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 68 S.Ct. 440, 92 L.Ed. 588 (1948):

Machines lend themselves *readily to*

> descriptions in terms of mechanical principles and physical characteristics. On the other hand, it may be that a combination of *314 strains of bacterial species, which strains are distinguished from one another and recognized in practice solely by their observed effects, can be definable reasonably only in terms of those effects.

Id. at 136-37, 68 S.Ct. at 444 (Burton, J., dissenting). Similarly, those skilled in the art of making monoclonal antibodies distinguish and define antigens based on their observed characteristics. Accordingly, the phrase "wherein said antigen is stage specific and not lineage dependent, and said antigen is also specifically bound by the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483" (the " 'wherein' clause") is a verbal attempt to describe a specific physical entity, which those skilled in the art now call the CD34 antigen.

The parties appear to agree that the "wherein" clause refers to the antigen now identified as CD34. CellPro contends that it does not agree and that the phrase refers only to the antigen identified by Civin as My-10. Those skilled in the art of making monoclonal antibodies, however, clearly understand that My-10 and CD34 are the same. The attorney prosecuting the application for the '204 patent argued that My-10 was becoming known in the art as CD34 as a result of the International Leukocyte Workshops. The examiner recognized this when she observed that claim 1 "limits the claimed monoclonal antibodies to species that react with a particular antigen (now identified as CD-34)." Furthermore, the testimony of Dr. James D. Griffin, one of plaintiffs' experts, and of Civin establish that My-10 and CD34 are the same. Griffin is a professor at Harvard Medical School and the Associate Director of the Division of Hematologic Malignancies at the Dana Farber Cancer Institute. Therefore, it appears that the "wherein" clause refers to CD34.

Assuming that My-10 is CD34, CellPro nevertheless objects to what it considers the removal of the phrase "stage specific" from claim 1 because it seeks an opportunity to prove that CD34 is not in fact stage specific. CellPro's argument is inapposite for two reasons. First, by construing the "wherein" clause, the court is not removing the language in that clause from the claims. Rather, it is determining the meaning of that language for the purpose of determining whether CellPro's devices infringe the patent. Thus, the phrase "stage specific" merely attempts to describe an aspect of the CD34 antigen at the time the patent issued, that it is was detectable on immature cells and not detectable on mature cells. To the extent the court previously construed the phrase "stage specific" to be inconsistent with the true characteristics of the CD34 antigen, that construction was incorrect.

The second reason CellPro's argument is inapposite is that the issue of whether CD34 is found on mature cells--and thus is not "stage specific" in CellPro's view--goes to whether the invention claimed in the '204 patent lacks utility or is inoperable, not to whether there is infringement. The utility of the '204 patent appears to derive from the fact that CD34 was detectable only on immature cells at the time the patent issued. Civin concluded from this fact that he could use antibodies to the CD34 antigen to label immature cells and separate them from mature cells. If CellPro can prove by clear and convincing evidence that CD34 antibodies cannot serve this function, then the '204 patent may be invalid for lack of utility or inoperability. This is not an issue of claim construction or infringement, however. If an antibody "specifically binds" to the CD34 antigen, it infringes claim 1 of the '204 patent whether or not that claim is invalid.

2) What is the meaning of "specifically binds"?

Griffin testified that "specifically binds" is synonymous with words such as "recognizes" and "adheres" in that it refers to the specific chemical interaction that occurs between an antigen and an antibody. He further testified that "specific binding" is in contrast to "nonspecific binding," which refers to the attachment of an antibody to an antigen due to some other factor, such as the stickiness of the antigen or cell. The specification and the

prosecution history of the '204 patent support this construction because the phrase "recognize" is used interchangeably with "specifically binds." In fact, the examiner herself altered the words "recognizes" and "recognized" *315 to "specifically binds" and "specifically bound" without any indication that the latter phrases implied a special meaning or limitation. Furthermore, the prosecution history of the re-examination of the '680 patent also differentiates specific binding from nonspecific binding in the way Griffin does. Thus, plaintiffs' proposed construction of "specifically binds" as referring to antigen-antibody recognition appears correct.

Plaintiffs' proposed construction is partially incomplete, however, in that it does not necessarily reflect an inherent limitation in the concept of antibody-antigen recognition. Griffin testified that a particular monoclonal antibody recognizes only one antigen. Therefore, the concept of "specific" binding in the '204 patent also refers to the fact that the claimed antibody only binds to CD34. The specification supports this limitation at column 2, lines 16-20:

> In one embodiment, the present invention provides a monoclonal antibody that recognizes an antigen on human pluripotent lymphohematopoietic stem cells, but does not recognize an antigen on normal, human mature lymphoid and myeloid cells.

Thus, the court will modify plaintiffs' proposed construction of claim 1 to state the following--any monoclonal antibody that binds only to the CD34 antigen through an antigen-antibody interaction.

CellPro argues that this construction of the phrase "specifically binds" removes two specific limitations from claim 1. The first such limitation is that the claimed antibody must "specifically bind" to an immature cell, which means that the antibody cannot bind to a mature human cell. Claim 1 does not speak in terms of the antibody binding to particular cells, however; it speaks in terms of the antibody binding to a particular antigen. This limitation is captured by the requirement that the claimed antibodies must bind only with CD34 and not another antigen.

When the '204 patent application initially was filed, claim 1 did refer to the antibody binding to immature cells and not to mature cells. The claims subsequently were rewritten to focus on the location of the antigen to which the antibody bound, rather than the type of cell to which the antibody bound. Therefore, CellPro's proposed claim limitation really reflects the utility and operability issues discussed above with respect to the location of the CD34 antigen. In other words, if an antibody binds only to the CD34 antigen through an antigen-antibody interaction, even if the CD34 antigen is found on a mature cell, that antibody infringes claim 1. Of course, if CellPro can prove by clear and convincing evidence that CD34 is found on mature cells, claim 1 of the '204 patent may be invalid as inoperable or lacking utility.

The second limitation CellPro proposes is that the claimed antibodies must "specifically bind" to an antigen on a human cell, which means that the antibodies cannot bind to an antigen on nonhuman cells. CellPro relies on the portion of claim 1 that describes the CD34 antigen as "on non-malignant, immature human marrow cells." It is clear, however, that this phrase does not attempt to describe every possible location of the CD34 antigen. For example, the specification itself teaches that CD34 is found on the KG-1a cell line, which contains malignant cells. Therefore, the claim language alone does not suggest that the claimed antibodies cannot bind to an antigen on nonhumans as long as that antigen is CD34.

CellPro also relies on a statement made by the prosecuting attorney during the reexamination of the '680 patent. In distinguishing an article by Castignola et al. entitled "Purification of Rat Pluripotent Hemopoietic Stem Cells" (the "Castignola article"), the attorney stated:

> Castignola, et al., is concerned with rat cells obtained by a method including separating bone marrow cells from rats treated with hydrocortisone on a density gradient and then using a fluorescence cell sorter to select

> cells showing high fluorescence with a fluorescent anti-Thy-1 antibody (specific for T cells).... Furthermore, there is no indication that the properties of human pluripotent stem cells are similar to those of the rat cells studied by Castignola, et al.

CellPro argues that this statement, in combination with the claim language, established a *316 limitation that the claimed antibodies cannot bind to an antigen on nonhuman cells.

This argument fails for two reasons. First, the examiner stated that Castignola et al. was not pertinent prior art, and thus she did not consider it in allowing the claims. Second, the prosecuting attorney was not discussing the meaning of the phrase "specifically binds" in the '204 patent or the binding properties of the claimed antibodies. Rather, he was arguing that the Castignola article does not teach that human stem cells may have an antigen that can be used to separate immature from mature cells to form a cell suspension as claimed in the '680 patent. The attorney never argued that the CD34 antigen is not on nonhuman cells, nor did he argue that the claimed antibodies only bind to an antigen on human cells. Consequently, the court will adopt the following construction of claim 1 of the '204 patent--any monoclonal antibody that binds only to the CD34 antigen through an antigen-antibody interaction.

b. Does CellPro's 12.8 antibody bind only to the CD34 antigen through an antigen-antibody interaction?

[13] The evidence offered at trial, including through CellPro's own experts, establishes that the 12.8 antibody binds to the CD34 antigen through an antigen-antibody interaction. CellPro does not appear to contest that evidence, nor could it given that its accused devices function on the basis that 12.8 is an antibody to the CD34 antigen capable of separating stem cells from mature cells. Rather, CellPro offered testimony at trial in support of three apparent infringement defenses.

In support of its first defense, CellPro offered evidence that the 12.8 antibody is an IgM antibody instead of an IgG antibody. Because claim 1 is not limited to IgG antibodies, this evidence is irrelevant to infringement.

In support of its second defense, CellPro offered evidence to establish that 12.8 binds to primate cells. There seem to be two noninfringement theories related to this evidence. The first is that the claimed antibodies cannot bind to a nonhuman cell or an antigen on a nonhuman cell. For the reasons set out above in the court's construction of claim 1, there is no such limitation in claim 1. The second theory is that 12.8 does not bind only to CD34. There was no testimony, however, to establish that the antigen to which 12.8 binds in primates is not CD34, and it does not appear that the jury could reasonably infer this conclusion from the evidence that was presented. Thus, the court must conclude that binding to primate cells is merely an extra feature of 12.8 that does not avoid literal infringement of claim 1.

In support of its third defense, CellPro offered the testimony of its expert Dr. Paul J. Simmons to establish that 12.8 binds to mature basophils. Simmons is the Chief Hospital Scientist at the Hanson Center for Cancer Research in Adelaide, South Australia. At trial Simmons presented data, in the form of histograms, that he recovered from his analysis of a cell suspensions created by the use of the 12.8 antibody and a control IgM antibody. According to his testimony, the difference in fluorescence between the suspensions created by the two antibodies demonstrates that 12.8 specifically binds to an antigen on basophils.

Plaintiffs have objected to the admission of this scientific evidence on the basis that it fails to satisfy the foundational requirements of Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993), and In re Paoli R.R. Yard PCB Litigation, 35 F.3d 717 (3d Cir.1994). Although plaintiffs appear to raise many valid arguments with respect to the methodology that Simmons followed, the court need not

reach the question of whether it should have excluded his testimony. Even if Simmons's testimony were admitted properly under Daubert and In re Paoli, there is a serious question as to whether the jury could rely solely on this evidence to find noninfringement of claim 1 of the '204 patent.

There seem to be three noninfringement theories related to this evidence. The first is that the claimed antibodies cannot bind to a mature cell. For the reasons set out above in the court's discussion of the phrase "specifically binds," there is no such limitation in claim 1. The second theory is that CD34 is *317 found on mature cells and thus is not "stage specific." For the reasons set out above in the court's discussion of the "wherein" clause, this argument goes to the validity of claim 1 and not to infringement of that claim. The third theory suggested by CellPro is that 12.8 does not bind only to CD34 but binds to some other antigen on mature cells. In order to find noninfringement based on this theory, the jury would have to infer from Simmons's testimony that when fluorescence testing indicated that 12.8 antibodies were attached to basophils, that those 12.8 antibodies were specifically bound to an antigen other than CD34.

Even if such an inference were reasonable, which is not entirely clear, it would be against the great weight of the evidence. On the one hand, there was no testimony that the antigen to which 12.8 allegedly bound was not CD34. Simmons testified that he never tested the antigen, even though he admitted that such testing is possible. Moreover, Griffin testified that monoclonal antibodies by definition only bind to one antigen, suggesting that if 12.8 did specifically bind to an antigen on a basophil, it had to be CD34. On the other hand, there is severe doubt as to whether the attachment identified by the Simmons's experiment was specific binding. All of the other expert testimony at trial, which was based on over a decade of experimental testing and verification, established that 12.8 specifically binds to CD34 on immature cells and does not bind to basophils and other mature cells. In addition, Simmons admitted that the control cells he was using were susceptible to becoming sticky under certain conditions that he could not verify, which suggests that the attachment he identified may not have been specific binding.

The great weight of the evidence in favor of infringement, in addition to the factors set out below, suggests that plaintiffs should be entitled to a new trial on the issue of whether the 12.8 antibody infringes claim 1 of the '204 patent. The plaintiffs will have the benefit of a proper claim construction and, consequently, a proper jury instruction at a new trial. In addition, a new trial will give the court an opportunity to make "a preliminary assessment of whether the reasoning or methodology under lying [Simmons's] testimony is scientifically valid." Daubert, 509 U.S. at 592-93, 113 S.Ct. at 2796; In re Paoli, 35 F.3d at 743. Finally, CellPro offered Simmons's testimony extremely late during discovery, and plaintiffs received many of the documents related to Simmons's testimony in the middle of the trial. Thus, a new trial will allow plaintiffs to prepare adequate cross-examination of Simmons, if necessary.

2. Has CellPro infringed or induced infringement of the claims of the '680, '994, and '144 patents?

The parties appear to agree that the determination of whether CellPro infringed or induced infringement of the claims of the '680, and '994, and '144 patents turns on whether CellPro's accused devices produce suspensions of stem cells that are "substantially free of mature lymphoid and myeloid cells." Plaintiffs argue that the court erred by failing to provide a more specific description of the phrase "substantially free." Plaintiffs then argue that when the claims of the '680, '994, and '144 patents are properly construed, more than sufficient evidence exists to support a verdict of infringement or induced infringement. CellPro once again argues that plaintiffs failed to meet their burden of proving infringement.

a. What is the proper construction of the claims of the '680, '994 and '144

patents?

Except with reference to the phrase "substantially free," the parties do not contest the court's construction at trial of the claims of the '680, '994, and '144 patents. Therefore, the court will continue to construe the terms "administering said cell suspension" and "an amount effective to effect such restoration" in the '144 patent in accordance with their ordinary meaning. The court will revisit the construction of the phrase "substantially free" because it appears that the court's construction of that phrase at trial was in error. In addition, the court will examine step (b) of claim 1 of the '994 patent on its own initiative in order to construe the language of that claim in accordance with the court's construction of claim 1 of the '204 patent.

*318 1) What is the meaning of the phrase "substantially free"?

[14] In their post-trial briefs, plaintiffs argue that the court should have given the jury some explanation of the phrase "substantially free," but they fail to offer any alternative construction. Based on plaintiffs' arguments before and at trial, the court assumes that plaintiffs seek to establish that "substantially free of mature lymphoid and myeloid cells" means at least 85-90% purity. The court is reluctant to impose mathematical certainty on an ambiguous term when a patent applicant has strenuously avoided doing so. See Johns Hopkins University, 894 F.Supp. at 827. The parties appear to agree, however, that the cell suspension required by the claims of the '680, '994, and '144 patents must contain no more than 10% mature lymphoid and myeloid cells. Moreover, this construction is consistent with the specification and the expert testimony offered at trial.

Although the specification does not provide a specific percentage required for a cell suspension to be "substantially free," it does give a reference by which one skilled in the art could ascertain such a percentage. The specification states at column 3, lines 62-67:

> Various assay techniques have been employed to test for the presence of the My-10 antigen, and those techniques have not detected any appreciable number (i.e. not significantly above background) of normal, mature human myeloid and lymphoid cells in My-10-positive populations.

In a deposition offered in connection with plaintiffs' motion for summary judgment before trial, Civin testified that a person of ordinary skill in the art would interpret the phrase "substantially free" in light of the practical limitations of the separation technique taught, which is the FACS method. He further testified that the FACS method would produce a cell population of 85-90% purity. This is consistent with the disclosure of a stem cell suspension of 90% purity in Table 9 of the specification.

At trial, experts for both plaintiffs and CellPro confirmed Civin's testimony. In response to cross-examination by CellPro on the meaning of the term "substantially free," plaintiffs' expert Griffin stated that "Let's say that everything over 10 [percent] would be outside that range." On direct examination on the issue of the meaning of the phrase "substantially free," CellPro's expert Dr. Kenneth D. Shortman testified:

> Well, in my laboratory, it--it would mean 97-percent-plus pure, I have to say. We seem to have--I have a bit of a lack standard here and everyone seems to have agreed around 10 percent.... Obviously, there's going to be a range of interpretations here, but I think 10 percent is the--the bottom end.

Shortman is a Senior Principal Research Fellow with the National Health and Medical Council in Australia and the head of a research unit called the Lymphocyte Differentiation Unit. Therefore, the court will construe the phrase "substantially free" to require a cell suspension of at least 90% purity. In other words, the cell suspension must contain no more than 10% mature lymphoid and myeloid cells.

2) How should the court construe claim 1 of the '994 patent?

[15] The parties have not discussed the construction of claim 1 of the '994 patent in their post-trial briefs. The court's altered

construction of claim 1 of the '204 patent, however, which extensively describes the antigen of interest and contains similar language such as "specifically binds" and "stage specific," suggests that the court should construe both claims consistently. Step (b) of claim 1 of the '994 patent states:

> (b) contacting said cell suspension with a monoclonal antibody to immature human marrow cells that is stage-specific and not lineage dependent so that said antibody binds to said stem cells, wherein said antibody specifically binds an antigen on human pluripotent lympho-hematopoietic stem cells said stem cells expressing an antigen that is specifically bound by the monoclonal antibody produced by the hybridomas deposited under ATCC Accession No. HB-8483 and does not specifically bind an antigen on mature, human myeloid and lymphoid cells; and

*319 For the reasons set out above in the court's construction of claim 1 of the '204 patent, it is clear that the antigen to which this step refers is the CD34 antigen and that the claimed antibodies must "specifically bind" to CD34 and not another antigen. Based on these facts, the court will construe step (b) to read as follows--contacting said cell suspension with any monoclonal antibody that binds only to the CD34 antigen through an antigen-antibody interaction.

b. Do the accused devices achieve purity of at least 90%?

Plaintiffs assert that CellPro infringed and induced infringement of claims 1-5 of the '680 patent and claims 1-3 of the '994 patent. Plaintiffs also claim that CellPro induced infringement of claims 1-4 of the '144 patent. CellPro argues that plaintiffs failed to meet their burden of proving infringement. In particular, CellPro argues that plaintiffs failed to offer any evidence of infringement because Griffin, plaintiffs' expert, did not test the accused devices. In addition, CellPro argues that even if the devices are capable of infringing use, it did not actually use or induce others to use the devices to infringe the Civin patents.

[16][17] Plaintiffs need not have tested the accused devices to prove infringement. See Allen Archery, Inc. v. Browning Mfg. Co., 819 F.2d 1087 (Fed.Cir.1987) (affirming a finding of infringement based on an advertisement of an infringing device in a catalog). Plaintiffs offered, and the court admitted, documents authored by CellPro establishing that CellPro and others used the accused devices to achieve suspensions of stem cells of 90% or greater purity. Plaintiffs' Trial Exhibit 48, a letter and brochure explaining the applications of the Ceprate LC, states that CellPro achieved purities of 91.5%, 91.6%, and 93.7% during experimental runs of the device. Furthermore, plaintiffs' trial exhibit 634, a clinical study protocol, states that clinicians achieved up to 95% purity during experiments with the Ceprate SC and then used the resulting cell suspensions for bone marrow transplants. These documents are admissions by CellPro that the accused devices are capable of infringing use and that CellPro and others actually used the accused devices to infringe the Civin patents.

[18] CellPro nevertheless argues that it did not induce others to infringe the Civin patents because it did not have "actual intent" to encourage infringement. See Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1469 (Fed.Cir.1990). Numerous documents authored by CellPro, however, encourage users of the accused devices to use the 12.8 antibody to create a suspension of purified stem cells. CellPro was aware of the Civin patents, yet CellPro's literature does not warn users of the existence of these patents or suggest that users achieve less than desirable purity to avoid infringement. Rather, the literature encourages users to achieve the highest purity possible because that is the most desirable result. Moreover, the references in the literature to greater than 90% purity confirm that CellPro was aware of the potentially infringing uses of the accused devices. These objective indicia are more than sufficient to establish CellPro's intent to induce infringement of the Civin patents and knowledge of likely infringement.

CellPro also argues that the 12.8 antibody

and the accused devices are "suitable for substantial non-infringing use" within the meaning of 35 U.S.C. § 271(c). This argument goes to whether CellPro contributorily infringed the Civin patents, not whether it induced infringement by others. Plaintiffs appear to have abandoned this issue, and thus the court will not address it.

[19] No reasonable jury could conclude that CellPro did not infringe and induce infringement of claims 1-5 of the '680 patent and induce infringement of claims 1-4 of the '144 patent. Thus, plaintiffs are entitled to judgment as a matter of law on these issues. With respect to the infringement and induced infringement of claim 1-3 of the '994 patent, plaintiffs are entitled to a new trial for the reasons set out above in the court's discussion of why plaintiffs are entitled to a new trial on the issue of infringement of claim 1 of the '204 patent.

*320 B. Did the Jury Properly Find That the Civin Patents Were Obvious?

[20][21][22] An inventor cannot obtain a patent "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which" the invention pertains. 35 U.S.C. § 103. Facts to consider when determining whether a patent was obvious include: 1) the scope and content of the prior art; 2) the level of ordinary skill in the art; 3) the differences between the subject matter claimed and the prior art; and 4) other objective indicia of nonobviousness. See Graham v. John Deere Co. 383 U.S. 1, 17-18, 86 S.Ct. 684, 693-94, 15 L.Ed.2d 545 (1966). CellPro has the burden of proving these facts by clear and convincing evidence. Greenwood v. Hattori Seiko Co., 900 F.2d 238, 241 (Fed.Cir.1990). The ultimate determination of obviousness, however, is a question of law. Graham, 383 U.S. at 17, 86 S.Ct. at 693-94; Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1547 (Fed.Cir.1983).

[23] Plaintiffs contend that CellPro's prior art references in support of its defense that the Civin patents were invalid as obvious were not properly before the jury. Plaintiffs also contend that even if these references were properly before the jury, CellPro failed to present testimony on each of the four factual predicates for a finding of obviousness. By contrast, plaintiffs argue that they offered "a wealth of evidence" regarding the objective indicia of nonobviousness. CellPro contends that its prior art references were properly before the jury and that it did present testimony on each of the factual predicates for establishing obviousness.

CellPro argues that two prior art references render the '204, '680, and '994 patents obvious: 1) Civin et al., "Characterization of Four Monoclonal Antibodies Reactive with Human Cell Subsets," Blood, 60(5):95a (abstract 1982); and 2) Koeffler et al., "An Undifferentiated Variant Derived from the Human Acute Myelogenous Leukemia Cell Line (KG-1)," Blood 56(2):265-273 (1980). CellPro cites a third document authored by Amato et al., entitled "Bone Marrow Transplants at the Ontario Cancer Institute," in support of its argument that the '144 patent was obvious. None of these documents was listed in the pre-trial order with respect to CellPro's invalidity defenses, however, as required by the court. Therefore, it appears that these documents were not properly before the jury on the issue of obviousness.

Even if the references were properly before the jury, CellPro never offered testimony to establish that these documents related to the obviousness of the Civin patents. In its post-trial brief, CellPro relies heavily on the testimony of its expert, Dr. Donald R. Sutherland, to establish the factual predicates for obviousness. Sutherland is a professor in the Department of Medicine in the University of Toronto, a Staff Scientist at the Otologist Bone Transplant Program at the University of Toronto, and a principal investigator in the Oncology Research Group of the Toronto General Hospital. During trial, however, CellPro explicitly disavowed that it was presenting Sutherland's testimony in support of its obviousness defense. Moreover,

Sutherland's expert report did not contain an opinion on the obviousness of the patent.

CellPro protests that the law does not require an expert opinion on the ultimate determination of obviousness, citing Mendenhall v. Cedarapids, Inc., 5 F.3d 1557, 1574 & n. 17 (Fed.Cir.1993), cert. denied, --- U.S. ----, 114 S.Ct. 1540, 128 L.Ed.2d 192 (1994). This argument misses the point, however. CellPro bears the burden of establishing by clear and convincing evidence the underlying factual predicates of obviousness in order to give the jury some guidance in making its determination. CellPro offered no testimony or evidence to meet this burden.

The great weight of the evidence suggests that none of the Civin patents were obvious to one skilled in the art at the time the patent was filed. CellPro argues that the prior art teaches the existence of the KG-1a cell line and the similarity between that cell line and immature cells. CellPro further argues that, according to Griffin's testimony, the Kohler/Milstein method of making monoclonal antibodies was well known. From *321 these facts, CellPro argues that it would have been obvious for one skilled in the art to make CD34 antibodies. CellPro's argument is inapposite, however, because it focuses on the method of making monoclonal antibodies, whereas the Civin patents are directed to the antibodies themselves and methods of using those antibodies. As the examiner succinctly stated during her examination of the '204 patent:

> While the KG-1a cell line which bears determinants recognized by the claimed antibodies was known and the methods of producing monoclonal antibodies were known, the identity of the particular antigen determinant identified by the claimed monoclonal antibodies was not disclosed by the ... [prior art]. One with ordinary skill in the art would not have a reasonable expectation of being able to identify and produce a monoclonal antibody to a previously unknown antigen.

In other words, one skilled in the art cannot make an antibody to an unknown antigen.

Secondary considerations of nonobviousness support the examiner's conclusion that Civin's inventions were not obvious to one skilled in the art. The prior art cited by CellPro identifies a long-felt but unsolved need--a way of separating and isolating stem cells, particularly for bone marrow transplants--that is satisfied by the inventions claimed in the Civin patents. Furthermore, Johns Hopkins's licenses of the Civin patents to Becton Dickinson, Baxter, Systemix, Applied Immune Sciences, and Dynal Corporation suggest the considerable commercial success of the patents. Finally, Civin's inventions appear to have been a major breakthrough in medical science, as evidenced by the fact that the scientific community heralded Civin's discovery when he first published his findings, that nearly 1500 scientific papers have been written on the topic of the CD34 antigen and CD34 antibodies, and that no person has since discovered an antibody useful for isolating stem cells.

CellPro's only remaining argument focuses on the discovery by a Dr. Tindle of a CD34 antibody independently of Civin's research. CellPro stresses the fact that Civin had access to this antibody before he published his paper in 1984. There is no evidence, however, to establish when Tindle discovered the CD34 antibody. Moreover, there is no evidence to suggest whether Tindle created a CD34 antibody on purpose or accidentally. The jury would have to infer from this evidence that Tindle was seeking an antibody to an antigen on stem cells, that he created such an antibody before Civin did, and that he was aware that he had created such an antibody.

CellPro makes the further assertion that substantial new evidence came out at trial that was not before the patent office examiner, thereby reducing its burden of proof, but it fails to identify any such evidence. In fact, it appears that all three of CellPro's prior art references were before the patent office. Thus, contrary to CellPro's assertion, its burden of proving facts in support of obviousness "is especially difficult" because the PTO considered all of the prior art cited by CellPro at trial. See Hewlett-Packard, 909 F.2d at

1467.

Given that CellPro argued obviousness to the jury based on prior art that was not properly identified in the pre-trial order and based on testimony that was not offered and admitted as relevant to the issues directed to obviousness, and given that the great weight of evidence suggests that CellPro has not met its burden of proving by clear and convincing evidence facts underlying obviousness, plaintiffs are entitled to a new trial on the issue of whether the Civin patents were obvious to one skilled in the art at the time the inventions were made.

C. Did the Jury Properly Find That the Civin Patents Were Not Enabled?

[24][25][26][27][28] Patent law requires an inventor to disclose the method of making a claimed invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains ... to make and use the same." 35 U.S.C. § 112. If the specification requires one skilled in the art to perform "undue experimentation" to practice the invention claimed in the patent, the patent is invalid as not enabled. In re Wands, 858 F.2d 731, 737 (Fed.Cir.1988). "The determination of what constitutes undue experimentation *322 requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." Id. Factors to consider include: 1) the amount 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. CellPro has the burden of proving these facts by clear and convincing evidence. Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 941 (Fed.Cir.), cert. denied, 498 U.S. 920, 111 S.Ct. 296, 112 L.Ed.2d 250 (1990). The ultimate question of whether the specification enables an invention claimed in the patent, however, is a question of law. Id.; Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed.Cir.1986), cert. denied, 480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987).

1. Is the '204 patent properly enabled?

[29] Plaintiffs argue that the "law of monoclonal antibody enablement" establishes that once a particular antigen is identified, the method of making an antibody to that antigen is enabled because those skilled in the art can use the Kohler/Milstein method with predictable success, citing Hybritech and Ex parte Erlich, 3 U.S.P.Q.2d 1011 (Bd.Pat.App. & Int.1986). Plaintiffs also observe that CellPro has failed to identify anything that Civin left out of the specification that would have enabled the '204 patent. CellPro argues that reasonable jurors could determine that the Civin patents required undue experimentation based on the evidence offered at trial.

a. Is there a "law of monoclonal antibody enablement"?

In Ex parte Erlich, the Patent Board of Appeals and Interferences (the "Board") discussed the concept of undue experimentation in the context of the field of making monoclonal antibodies. The Board stated that "once the antigen of interest is selected, the use of that antigen in the known method of Kohler and Milstein will result in the expected hybrid cell lines and the specific monoclonal antibodies." Id. at 1015. The Board further observed that although the Kohler/Milstein method might be "tedious and laborious," such experimentation is nevertheless "routine." Id. at 1016. Subsequent decisions by the Board and the Federal Circuit have confirmed that the methodology for making monoclonal antibodies was generally known and routine by 1980, well before Civin's inventions. See In re Wands, 858 F.2d at 737-740; Hybritech, 802 F.2d at 1384; Ex parte Sizto, 9 U.S.P.Q.2d 2081 (Bd.Pat.App. & Int.1988); Staehelin v. Secher, 24 U.S.P.Q.2d 1513, 1517 (Bd.Pat.App. & Int.1992).

[30] These opinions do not establish, however, that all monoclonal antibody patents

are enabled merely by disclosing the antigen to which the antibodies bind. A determination of enablement still depends on the specific facts of each case. See, e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1557 (Fed.Cir.1983), cert. denied, 469 U.S. 851, 105 S.Ct. 172, 83 L.Ed.2d 107 (1984). For example, in Hybritech the Federal Circuit observed that "there was not a shred of evidence that undue experimentation is required by those skilled in the art to practice the invention." Id. at 1384. In In re Wands the Federal Circuit stated that "there has been no claim that the fusion step should be more difficult or unreliable ... than it would be for other antigens." Id. at 740. By contrast, CellPro has claimed that it takes undue experimentation to produce an antibody to the CD34 antigen. Thus, the court must carefully examine the evidence offered at trial in support of this argument.

b. Did CellPro offer clear and convincing evidence in support of its assertion that the '204 patent is not enabled?

CellPro admits that the specification of the '204 patent enables one skilled in the art to make Civin's My-10 antibody. CellPro nevertheless argues that the specification does not enable one skilled in the art of making all antibodies to the CD34 antigen. CellPro offered four types of evidence in support of this argument. First, it offered evidence to show that Civin's laboratory was unable to *323 make another antibody to the CD34 antigen. Second, it offered the testimony of Sutherland who stated that he failed to make an antibody to the CD34 antigen. Third, it offered evidence that few antibodies to CD34 were produced in the immediate five years after Civin first published his findings in 1984. Fourth, it offered testimony to establish that two of the three techniques disclosed in the specification do not work.

As to the failures to make a CD34 antibody in Civin's laboratory, CellPro failed to offer evidence that many of the people working in the lab were of ordinary skill in the art. Testimony at trial established that a person skilled in the art of making monoclonal antibodies must have a bachelor's degree in the appropriate scientific field and must have made a monoclonal antibody at least once. Sutherland stated that he assumed those in the lab would be of ordinary skill because of Civin's reputation and because he was supervising their work. Testimony established, however, that many of the people working in the lab were undergraduates or had never made a monoclonal antibody, as evidenced by the fact that most never even achieved a working fusion as the first step in making a monoclonal antibody. Even Dr. Alfred Nisonoff, one of CellPro's experts, admitted that Civin may have hired the workers in his lab simply for them to practice lab technique, not because they had extensive training and experience in making monoclonal antibodies. Nisonoff is a Professor of Biology in the Rosensteil Research Center at Brandeis University. Moreover, testimony established that many of these workers were not using the KG-1a cell line as the immunogen as suggested by the specification. Thus, it is not clear that this evidence is relevant to a determination of enablement, which looks at the adequacy of the actual disclosure from the perspective of one skilled in the art.

As to Sutherland's failure to make a CD34 antibody, testimony established that many of his experiments also failed to produce a working fusion. This either suggests that he was not skilled in the art at the time of his experiments or that his laboratory techniques were somehow deficient. It does not tend to suggest that the patent fails to disclose sufficient information. Of the four successful fusions Sutherland achieved, he did not manage to make a monoclonal antibody. Sutherland did not use the screening technique disclosed in the specification, however. Thus, as with the failed experiments in Civin's lab, it is not clear how relevant Sutherland's failures are to whether the actual specification enables the '204 patent.

As to the evidence that only a few CD34 antibodies were produced in the first five years after Civin published his findings, this fact alone does not suggest nonenablement.

Sutherland testified that he did not consider any antibodies made after 1988 because he would have expected an explosion of monoclonal antibodies with a proper disclosure. Sutherland's bright historical line rather conveniently ignores the approximately 20 to 30 CD34 antibodies that were made after 1988. It also ignores the fact that the 12.8 antibody, which was produced before 1988 and which is the most unlike other antibodies in terms of affinity and structure, was made following Civin's teachings. CellPro argues that plaintiffs did not demonstrate that the antibodies made after 1988 were made following Civin's teachings. This argument ignores the fact that CellPro bears the burden of proving nonenablement, not the other way around.

[31] As to the argument that two of the three disclosed methods of making monoclonal antibodies do not work, plaintiffs appear to concede this. This fact cannot by itself establish nonenablement, however. "The enablement requirement is met if the description enables any mode of making and using the claimed invention." Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533 (Fed.Cir.1991). Therefore, as long as the remaining disclosed method enables the invention claimed in the '204 patent, then the enablement requirement is met.

Even if one considers all of the above testimony offered by CellPro, the weight of the evidence suggests that the '204 patent is enabled. Despite the fact that CellPro's experts claim that the '204 patent in not enabling, none of them can identify anything that is missing from the specification. By contrast, the specification states that Civin's *324 hybridoma is on deposit for others to utilize. In addition, the specification describes the entire fusion process, including the immunogen, which is also on deposit, the specific type of mice immunized, and the use of the methodology devised by Kohler and Milstein. The mere fact that the Kohler and Milstein method is "tedious and laborious" does not make it use undue experimentation as CellPro appears to suggest. See Ex parte Erlich, 3 U.S.P.Q.2d at 1016. Rather, CellPro must identify some specific proof that the use of the Kohler/Milstein method is more unpredictable or more unreliable with respect to CD34 than it is with other antigens.

The only evidence offered at trial in support of the notion that the Kohler/Milstein method is less predictable when applied to the CD34 antigen comes from the testimony of Sutherland and Civin. Both of these men testified that CD34 is only weakly immunogenic, which means that it is more difficult to obtain a working fusion to produce CD34 antibodies than it is to produce antibodies to other antigens. There does not appear to be any additional step that can be taken, however, to improve the success rate of the Kohler/Milstein method as applied to the CD34 antibody. CellPro argues that over the course of time advancements in the art must surely have occurred, but it never identifies any such advancement.

Given the general unpredictability of making monoclonal antibodies, the lack of awareness in the art of improving that process with respect to the weak immunogenicity of the CD34 antigen, the tenuous relevance of the failures by Sutherland and Civin's lab, and the number of CD34 antibodies that have been made, it is not clear that CellPro has proven that the '204 patent is not enabled. Therefore, the court will grant plaintiffs a new trial on this issue.

2. Is the '680 patent properly enabled?

[32] CellPro attempts to emphasize the breadth of the claims in the '680 patent as a basis for finding nonenablement. For example, CellPro argues that claim 1 purports to claim all human cell suspensions that are substantially free of mature lymphoid and myeloid cells, regardless of the size of such suspension, the method by which such suspension is achieved, the particularized signature of the particular antibody used, or whether or not the antibody bound to the cells is removed. Plaintiffs admit that these facts are true but argue that they are irrelevant.

[33] The court agrees with plaintiffs. This is

not a case in which the patent claims a range of biological products and only provides a working example with respect to a few of those products, without regard to the difficulty involved with producing the undisclosed products. See Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1212-1214 (Fed.Cir.), cert. denied, 502 U.S. 856, 112 S.Ct. 169, 116 L.Ed.2d 132 (1991). The '680 patent claims a specific product, a purified suspension of stem cells, and CellPro has admitted that the specification enables one skilled in the art to achieve such a suspension by using the My-10 antibody. The specification need only enable one mode of making the claimed invention. Engel Indus., 946 F.2d at 1533. The fact that others may find an alternative method of making the claimed suspension in the future is not relevant.

CellPro also argues that the specification fails to disclose any working examples of a stem cell suspension of 90% purity as claimed in the patent. CellPro's argument is inapposite for two reasons. First, illustrative examples are not required as long as objective enablement is satisfied. In re Wright, 999 F.2d 1557, 1561 (Fed.Cir.1993). Second, as set out in the court's construction of the phrase "substantially free," Table 9 does provide an example of 90% purity. CellPro nevertheless attempts to argue, based on Sutherland's testimony at trial, that Table 9 only presents a purity of 84%.

The footnote to Table 9 states that 3% of the separated cells were mature neutrophils, 6% were mature monocytes, 1% were mature lymphocytes, 84% were "primitive blast" cells, and 6% were promyelocytes. Sutherland testified on cross-examination that, based on this footnote, Table 9 recited 90% purity. On redirect examination, he stated that Table 9 recited 84% purity if one did not count the 6% promyelocytes. Promyelocytes, also known as premyelocytes, are partially *325 differentiated cells, but they lack the characteristics of mature granulocytes. The footnote itself differentiates the blast cells and promyelocytes, which constitute 90% immature cells, from the remaining 10% mature cells. Therefore, the jury could not rely upon Sutherland's incorrect reading of the specification in order to support a finding of nonenablement.

The court further observes that even if it were to accept CellPro's argument that Table 9 discloses only 84% purity, it would construe the "substantially free" limitation consistent with that percentage for the purposes of enablement and infringement. Thus, the '680 patent would still be enabled, and CellPro would be infringing over an even wider range of purities.

CellPro individually attacks claim 5 of the '680 patent, which requires that the stem cell suspension have "the ability to restore the production of lymphoid and hematopoietic cells to a human lacking said production" as lacking sufficient enablement. Sutherland opined that this claim limitation was not enabled because the specification did not disclose a working example of using the stem cell suspension to restore the ability of a patient to make blood. As noted above, illustrative examples are not required to enable a patent. In re Wright, 999 F.2d at 1561. Regardless, it appears that this phrase in the claim merely refers to the innate quality of human stem cells. The specification states at column 3, lines 13-17:

> Stem cells have the ability to restore, when transplanted, the production of hematopoietic and lymphoid cells to a patient who has lost such production due to, for example, radiation therapy.

Moreover, this characteristic of stem cells is well known in the art. That is why scientists have been seeking a method of isolating such cells for the purpose of conducting bone marrow transplants.

Dr. Oliver W. Press, the Acting Program Director of the High-Dose Chemotherapy and Bone Marrow Transplant Unit at the University of Washington Medical Center and another of CellPro's experts, opined that claim 5 was not enabled because it did not allow one skilled in the art to adequately perform a bone marrow transplant. Claim 5 contains no such limitation, however. Only the '144 patent is

directed to using a purified suspension of stem cells in a bone marrow transplant procedure. Claim 5 of the '680 patent merely provides for the stem cell suspensions themselves, which may be useful in research applications as well as in clinical medical applications.

For the reasons set out above, no reasonable jury could conclude that claims 1-5 of the '680 patent are invalid for lack of enablement. Thus, plaintiffs are entitled to judgment as a matter of law on this issue.

3. Is the '994 patent properly enabled?

[34] CellPro argues that the specification of the '994 patent does not enable the broadest scope of claim 1--the use of any CD34 antibody to isolate a purified stem cell suspension. Specifically, Sutherland testified that claims 1-12 do not teach how to achieve a "substantially free" cell suspension, that claims 8, 11, and 12 do not provide a working example showing the claimed method was actually performed on a human donor, and that claims 1-4, 6, and 7-11 cover the use of nonenabled antibodies (any antibody other than My-10). In addition, Shortman testified that the patent does not detail the engineering necessary to build a separation column, that the rosetting, panning, and column techniques identified in specification are insufficiently described, and that the method does not provide a large enough scale for successful clinical applications.

For the reasons set out in the court's discussion of why the '680 patent is enabled, the arguments with respect to the "substantially free" limitation, the lack of a working example of a donor, and the inapplicability of the method to clinical applications are inapposite. In other words, the patent enables a stem cell suspension of 90% purity, working examples are not required as long as objective enablement is met, and the '994 patent is not limited to clinical uses. Moreover, claims 8, 11, and 12 only require that one seeking to obtain a purified cell suspension draw blood from a donor, pass it through a separation column, and then return the blood to the *326 donor. This is a simple process well known in the art.

With respect to the engineering and alternative methods arguments, the court observes that the '994 patent is not directed to a separation column but a method of separation. The specification references a preexisting machine, the FACS machine, that can perform the required functions. The fact that the remaining suggestions, such as panning and rosetting, may be nonenabled is irrelevant. Engel Indus., 946 F.2d at 1533.

As to the final argument with respect to the nonenablement of antibodies other than My-10, for the reasons set out in the court's discussion of why plaintiffs are entitled to a new trial on the issue of whether the '204 patent is enabled, plaintiffs are entitled to a new trial on the issue of whether antibodies other than My-10 are enabled for use in the '994 patent.

4. Is the '144 patent properly enabled?

[35] CellPro presents many similar theories as to why the '144 patent is invalid for lack of enablement: 1) that the specification does not enable the "substantially free" limitation; 2) that the specification does not enable antibodies other than My-10; and 3) that the specification does not present a working example of a bone marrow transplantation. For the reasons stated above, these arguments are insufficient to support the jury's verdict and would suggest that plaintiffs are entitled to a new trial on this issue.

CellPro presents additional theories in support of the jury's finding of nonenablement, however, that require greater scrutiny. First, Press testified that the patent would require undue experimentation as to the "effective amount" of stems cells required to perform a transplant. Second, Shortman and Sutherland testified that a person isolating cells by means of a FACS machine would not be able to achieve a number of cells sufficient to support clinical uses of the stem cell suspensions. Third, Press testified that the '144 patent was nonenabled because it did not provide a means for removing the

antibody from the stem cell prior to the transplant.

a. Does the '144 patent sufficiently teach what is "effective amount" of stem cells?

Step (b) of claim 1 of the '144 patent requires the collection of a purified suspension of stem cells in an "amount effective" to restore a patient's ability to produce lymphoid and hematopoietic cells. The specification states:

> Precise, effective quantities can be readily determined by those skilled in the art and will depend, of course, on the exact condition being treated by the therapy. In many applications, however, an amount containing approximately the same number of stem cells found in one-half to one liter of aspirated bone marrow should be adequate.

Press testified that, based on his experience, he would prefer to process 1 to 1 1/2 liters of bone marrow in order to perform a transplant, although the ultimate volume required depends on factors such as the patient's age and prior exposure to chemotherapy. Press also testified that "there is a certain level of unpredictability" in the art of stem cell transplantation.

Plaintiffs attack Press's testimony in a number of ways. First, they argue that Press's figures overlap Civin's at the 1 liter mark. Second, they argue that CellPro documents acknowledge a range of 1/2 to 1 liter as being appropriate. Third, they argue that a person skilled in the art, knowing that separation devices yield less than 100% stem cells, would process more than 1 liter of bone marrow to end up with the number of stem cells in 1 liter. Fourth, they argue that Press did not testify as to whether a practitioner skilled in the art of bone marrow transplant in 1984 would know sufficient information to apply the patent without any additional disclosure.

CellPro's main argument appears to be that the specification requires undue experimentation to determine the amount of cells necessary. Enablement is not precluded by the necessity for some experimentation, however, as long as the amount of experimentation is reasonable given the nature of the invention and the state of the art. In re Wands, 858 F.2d at 737. In this case, it is *327 not clear that CellPro has proven by clear and convincing evidence that more than 1 liter's worth of cells is required for a successful transplant. Even if such an amount is required, however, the specification provides sufficient guidance in that direction by teaching a range of 1/2 to 1 liter. Moreover, Press admitted that there is unpredictability in the art and that many factors concerning the patient's condition need to be taken into account. It appears from his testimony that these factors are well known to physicians performing bone marrow transplants and that they do not constitute undue experimentation. Thus, the '144 patent sufficiently teaches an "effective amount" of stem cells.

b. Does the '144 patent sufficiently teach how to obtain an "effective amount" of stem cells?

CellPro focuses the majority of its nonenablement argument with respect to the '144 patent on whether the specification sufficiently teaches how to obtain an "effective amount" of stem cells for transplantation. CellPro presented an internal Baxter memorandum stating that Baxter had abandoned the use of the My-10 antibody for clinical cell transplantation applications. Shortman testified that the separation techniques identified in the patent would not be sufficient for clinical applications. In particular, he testified that panning was too variable, that column technology would require too much experimentation, that rosetting would not actually isolate cells, and that FACS sorting was impractical given its slow speed. Finally, CellPro argues that the substantial work required to produce its avidin/biotin column demonstrates the lack of enablement.

[36][37] CellPro's arguments ignore the appropriate legal standards. "Patents are not production documents, and nothing in the patent law requires that a patentee must

disclose data on how to mass produce the invented [process]...." Christianson v. Colt. Indus. Operating Corp., 822 F.2d 1544, 1562 (Fed.Cir.1987), vac'd on other grounds, 486 U.S. 800, 108 S.Ct. 2166, 100 L.Ed.2d 811 (1988). Moreover, the fact that others have developed commercial embodiments of the claimed invention is irrelevant. See Hormone Research Foundation v. Genentech, Inc., 904 F.2d 1558, 1568 (Fed.Cir.1990), cert. dismissed, 499 U.S. 955, 111 S.Ct. 1434, 113 L.Ed.2d 485 (1991). Thus, Civin need not have disclosed how to provide sufficient stem cell suspensions for large-scale clinical applications. It is sufficient that he disclosed one method, FACS sorting, that can provide sufficient cells for a stem cell transplant. Engel Indus., 946 F.2d at 1533.

CellPro attempts to argue that FACS sorting is not sufficient, but it did not prove this by clear and convincing evidence. Miller, one of CellPro's own experts, testified on direct that "I don't doubt you could do it on one patient here or there" using FACS sorting. This is all that is required for enablement. In addition, plaintiffs offered documents establishing that stem cells are frozen prior to transplantation, thus enabling practitioners to accumulate a sufficient number of cells using the FACS technology. At best, CellPro has proven that FACS sorting is impractical from a time and money perspective, not that it is impossible or requires undue experimentation. Thus, the '144 patent sufficiently teaches how to achieve an "effective amount" of stem cells for a bone marrow transplant.

c. Is the '144 patent nonenabled because it does not teach how to remove the antibody from the stem cells prior to transplantation?

CellPro argues that the '144 patent's failure to disclose a method for removing the antibody from the stem cell prior to transplantation renders the patent nonenabling. This is a curious argument given that the patent claims contain no such limitation. CellPro's argument appears to concern the issues of operability--whether the invention fails to achieve its goal of restoring a patient's ability to produce blood cells or whether it harms the patient more than it helps--or failure to disclose the best mode--by omitting a necessary yet nonclaimed element--rather than the issue of enablement.

The court further observes that even if this contention is relevant to enablement or inoperability, CellPro's evidence was shaky at best. Shortman testified that it would be "preferable" to remove the antibody from the *328 stem cells because the immune system might attack and destroy the cells. He admitted on cross-examination, however, that he had never tested CD34 antibodies for this possibility nor had he read of this concern in any sources. In addition, CellPro admitted the following with respect to the use of its own avidin/biotin technology in its Interrogatory responses, which plaintiffs offered at trial:

> Most target cells have antibody left on them after processing. We estimate that about 10 percent to 30 percent of the primary antibody remains on the cells after processing. We don't believe it affects cell function based on CFC data which demonstrates healthy growth under short-term culture conditions, and clinical engraftment, which indicates normal hematopoietic development in maturation in vivo.

CellPro has not proven by clear and convincing evidence that the removal of the antibody from the stem cells is required for a successful transplantation either by the claims or in practice. Thus, the '144 patent cannot be nonenabling for failing to provide a method of removing the antibody from the cells.

III. CONCLUSION

For the reasons set out above, plaintiffs are entitled to judgment as a matter of law on the following issues: 1) infringement and induced infringement of the '680 patent; 2) induced infringement of the '144 patent; and 3) enablement of the '680 patent.

For the reasons set out above, plaintiffs are entitled to a new trial on the following issues: 1) whether the '204 and '994 patents are

infringed; 2) whether the '204, '680, '994, and '144 patents are obvious; and 3) whether the '204, '994, and '144 patents are enabled. In addition, the court will submit to the jury the issue of infringement under the doctrine of equivalents on all of the Civin patents in accordance with Hilton Davis.

Plaintiffs have raised a number of other grounds in support of their motion for a new trial. Because the court has granted judgment as a matter of law or a new trial on each of the issues decided by the jury, it need not reach these remaining grounds.

The court will issue an Order in accordance with this Opinion.

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