May 7, 1997

Wendy Baldwin, Ph. D.
Deputy Director
Office of Extramural Research
National Institutes of Health
Building 1 Room 144
One Center Drive, MSC 0152
Bethesda, MD 20892

Re: Petition of CellPro, Incorporated

Dear Dr. Baldwin:

This letter is submitted on behalf of the Johns Hopkins University ("Hopkins") in response to your letter dated March 21, 1997 enclosing a petition of CellPro, Incorporated ("CellPro") to the Department of Health and Human Services ("DHHS"). We understand that your letter requests informal comments on the petition pursuant to 37 C.F.R. § 401.6(b), and that it does not constitute notice of the initiation of a formal proceeding pursuant to § 401.6(b) of the Regulations.[1]

Executive Summary

Hopkins opposes CellPro's petition requesting that DHHS exercise "march-in" rights under the Bayh-Dole Act, 35 U.S.C. §§ 200 et seq., to provide CellPro a compulsory license under patents owned by Hopkins. Hopkins long ago took "effective steps to achieve practical application" of the patented inventions, and no action on the part of the agency is necessary "to alleviate health or safety needs" of the public. 35 U.S.C. § 203(1) (a) and (b). Initiation of a march-in proceeding in these circumstances would be unwarranted and inconsistent with the Bayh-Dole Act's objective of encouraging nonprofit institutions to commercialize inventions through voluntarily negotiated patent licenses.

Hopkins' patented inventions for the first time enabled clinicians to purify hematopoietic stem cells, the master cells from which all types of cells in the blood and immune system derive. The inventions grew out of research conducted in the early 1980s at Hopkins' School of Medicine

---

[1] On May 2, 1997, Hopkins received a copy of a 39-page supplemental filing by CellPro in support of its petition. Hopkins has not had an opportunity to review and respond to CellPro's new filing. This letter responds to CellPro's original petition, and Hopkins will address the substance of the new filing at a later date.

by Dr. Curt Civin, now Professor and Director of Pediatric Oncology. One of the patents provides monoclonal antibodies that specifically bind to a newly discovered antigen, now known as the "CD34 antigen," that is expressed on the surface of stem cells. The other patent provides a highly purified suspension of stem cells, which can be made using the patented CD34 monoclonal antibodies in combination with known methods of cell separation.

Consistent with the Bayh-Dole Act's emphasis on bringing important inventions such as these to practical application, Hopkins took prompt steps to license out the technology for commercial development. Two such licensees, Becton Dickinson and Company and Baxter Healthcare Corporation have developed valuable new products that make use of the patented inventions in diagnostics and therapeutic procedures. Baxter's Isolex® 300 Stem Cell Separation System is used today in stem cell transplants across the country in FDA-approved clinical trials, and it is commercially available in Europe after having received regulatory approval there in 1995. In February, based on the success of its clinical trials, Baxter requested FDA approval for marketing of the Isolex® 300 system in the United States.

In March 1997, a unanimous federal jury determined that CellPro had willfully infringed Hopkins' patents in order to develop its Ceprate® SC system for stem cell separation. CellPro's SC product performs the same function as Baxter's Isolex® system: it processes blood or bone marrow using Hopkins' patented CD34 monoclonal antibodies in order to provide an enriched suspension of stem cells. In rendering its verdict, the jury determined that CellPro had no good faith basis to believe it had a lawful right to use the patented inventions in its product. To put it bluntly, the jury found that CellPro's SC system uses patented technology stolen from Hopkins.

CellPro filed its petition to this agency after refusing, on three occasions, to accept a license under the Hopkins patents on terms accepted by other companies, after flagrantly infringing the patents without payment of any royalties to Hopkins and its authorized licensees, and after forcing them to incur millions of dollars in litigation costs to defend the patents against CellPro's bad faith attack. The predicament in which CellPro now finds itself is the result of a calculated business decision aimed at maximizing the financial return to its management and its investors, without regard to Hopkins' patent rights or the risks associated with its "winner-take-all" litigation strategy.

CellPro seeks to justify its petition on the ground that the federal court's ruling in this case will deprive cancer patients of access to needed treatment. CellPro has made this assertion the centerpiece of a media barrage that has needlessly and irresponsibly created anxiety among cancer patients and their families. CellPro's assertion is untrue:

- As of this date, the federal court has imposed no restriction on CellPro's continued provision of the Ceprate® SC system for use in clinical trials or CellPro's sale of the

system for the narrow use authorized by the limited FDA approval CellPro received in December. The court is not expected to act until sometime in the summer, and any attempt to second guess the terms of an order that may be entered would be premature.

- Hopkins, Becton and Baxter have voluntarily asked the court to stay any injunction that is entered to assure that there will be no gap in patient access to the patented stem cell technology pending FDA approval of Baxter's Isolex® 300 system (or an alternative system licensed under the patents).

- Under the proposal, CellPro will be permitted to continue selling the Ceprate® SC device and disposable supplies until the FDA approves Baxter's system and for a phase-down period thereafter.

- CellPro will also be permitted to continue all current clinical trials and all future clinical trials authorized by the FDA as of the date Baxter's system is approved.

- Where CellPro makes no incremental profit on supplies furnished to hospitals in support of clinical trials, CellPro will not be required to make any royalty or other payment despite its infringement of Hopkins' patents.

In Part I below, we demonstrate in further detail that there is no public health justification for the unprecedented step CellPro asks DHHS to take.

In Part II, we set out in detail the background of the inventions, the extensive investment and product development activities of Hopkins' authorized licensees, and the calculated business decision of CellPro to ignore Hopkins' patent rights and initiate litigation in a bad faith attempt to avoid payment of royalties for use of the patents. In these circumstances, exercise of march-in rights to grant a compulsory license to CellPro would have a devastating impact on the ability of Hopkins and other nonprofit institutions to bring advances in medical technology to practical application through the licensing of patent rights to private companies whose investments depend on the integrity of the patent system.

In Part III, we provide a point-by-point response to the factual contentions made in CellPro's petition. As will be seen, CellPro's petition is riddled with errors, half truths, and outright misstatements of fact. It was submitted to DHHS just as Hopkins and its licensees were commencing trial against CellPro in Delaware, without awaiting the jury's verdict. CellPro's petition contains no explanation as to why, if there were merit to CellPro's petition, it did not seek the exercise of march-in rights to obtain a license under the patents years ago, before it began infringing. The inference is inescapable that CellPro's goal was to avoid paying any royalties to Hopkins and its licensees, whether under a negotiated license or under a forced license from

DHHS, by mounting an aggressive and wholly unfounded challenge to the patents in litigation. Only when it recognized that its litigation strategy had failed and that it was about to face the legal consequences of its willful misconduct did it suddenly turn to DHHS for a license. Hopkins trusts that DHHS will not permit the provisions of the Bayh-Dole Act to be so blatantly manipulated in the self-interest of a willful patent infringer.

I. Initiation of a March-In Proceeding is Not Necessary to "To Alleviate Health or Safety Needs."

1. *CellPro's petition is premature.*

As of this date, the federal court has not determined what form of equitable relief, if any, will be ordered against CellPro based upon its infringement of Hopkins' patents. Because there are other matters in the case that must be taken up first, the court is not expected to rule on the issue of an injunction until June or July. CellPro has opposed the entry of any form of injunction, and if it prevails, the issue presented by its petition will be moot. Furthermore, in accordance with federal law, the court will consider the public interest in fashioning any remedy for infringement of the patents, and CellPro has presented to the court the same public health arguments, and the same supporting materials, that it has presented to DHHS. For these reasons, CellPro's assertion that initiation of a march-in proceeding is necessary to the public health is premature, and its petition should be denied for that reason alone.

2. *Hopkins and its licensees are committed to assuring that there will be no gap in patient access to the patented stem cell separation technology.*

In its submissions to DHHS and in its public statements, CellPro has charged that Hopkins and its licensees are asking the court to shut down CellPro's clinical trials and deprive cancer patients of needed treatment. CellPro knows that this is untrue, yet it has continued its reckless charges unabated, seemingly without concern for the anxieties it has created among patients and their families.

Hopkins and its licensees are distinguished and responsible institutions, each with a long heritage of dedication to patient care. In asking the court to enforce Hopkins' patent rights, they are committed to the principle that no patient in need will be deprived of the stem cell technology that Dr. Civin developed at Hopkins and made available to the public by the disclosure of his inventions. If the court's order leaves any gap in patient care, they are prepared to seek modification of it as necessary to fulfill this principle.

That being said, CellPro cannot expect to continue infringing Hopkins' patents indefinitely. CellPro is not the only United States company capable of manufacturing a safe and effective system for purifying stem cells. In this case, both CellPro and Baxter have developed stem cell separation systems: CellPro's infringes and Baxter's does not. We ask CellPro to work with us responsibly to devise an order that will assure uninterrupted patient access to the technology, while also protecting Hopkins and its licensees from continued wrongdoing on CellPro's part.

3. *The proposed order will not interrupt CellPro's clinical trials.*

The main thrust of CellPro's public health argument is that the federal court's order will force it to shut down some sixty ongoing clinical trials. The clinician declarations CellPro recently submitted in support of its petition all make this assumption. However, Hopkins and its licensees do not propose to interrupt any CellPro clinical trials, as long as there is no FDA-approved, licensed alternative system available, and if the court orders otherwise, they will not seek to enforce that portion of the order.

In considering CellPro's clinician declarations, DHHS should take note of the fact that the majority of them were signed and dated before plaintiffs in the litigation even submitted their motion papers in support of injunctive relief. CellPro simply told the clinicians to assume the worst, and they did. The clinicians gave these declarations having no idea that plaintiffs intended to propose a partial stay of the injunction pending FDA approval of Baxter's Isolex® system.

When plaintiffs did submit their papers, CellPro unfairly seized on language in the initial draft of the proposed order relating to CellPro's commercial sales, claiming that the price protection proposed with respect to those sales was intended to shut down clinical trials and force CellPro to "confiscate" its device from hospitals using it. The proposed order said nothing of the kind, and plaintiffs have since revised it to remove any doubt. The current draft, which plaintiffs will submit to the court shortly, provides that under the stay, CellPro may continue through to completion any clinical trial approved by the FDA and an IRB as of now or at any time in the future, up to the date Baxter's system (or another licensed alternative) receives FDA approval. See Exh. I.

4. *CellPro's FDA approval to market the Ceprate® SC system for a narrow indication does not affect its status in clinical trials.*

CellPro's public health arguments put great emphasis on the status of the Ceprate® SC system as an "FDA-approved" device. This argument is misleading. In December 1996, the FDA approved the Ceprate® SC system only for use in autologous (self) transplants and only for use in processing bone marrow, as distinguished from peripheral blood. See Exh. O.

CellPro's FDA approval is thus for a very narrow indication. Dr. James Vredenburgh of Duke Medical Center has estimated that at least 85% of transplants today use peripheral blood rather than bone marrow as the source of stem cells. Vredenburgh Decl., ¶7.[2] Aspirating bone marrow from patients is painful and unpleasant, and doctors avoid it whenever possible.

As discussed below, Baxter's pending application to the FDA for pre-market approval of the Isolex® 300 system covers autologous stem cell transplantation using peripheral blood. CellPro, by contrast, has not as of this date even applied for FDA approval for this broader use of its system.

CellPro has argued in court and in numerous public statements that the FDA approval of its device allows clinicians to use it "off-label," that is, for indications other than the narrow indication approved by the FDA in December. In so promoting its device, CellPro appears to be acting in violation of federal law and regulations that forbid promotion of regulated devices for uses other than those that are approved.

The FDA's disapproval of CellPro's attempts to promote its Ceprate® SC system for indications other than autologous bone marrow transplantation was communicated to CellPro by the FDA earlier this year. The FDA described CellPro's "off-label" promotion as "false and misleading," amounting to "misrepresentations" that "misbrand" the product. See Exh. P. The FDA thus has made abundantly clear that for purposes of the clinical trials currently sponsored by CellPro, or any contemplated future trials involving, for example, the use of peripheral blood rather than bone marrow as the source of stem cells, the Ceprate® SC system is an "experimental" device, which has not been proven to be safe and effective. See also Preti Decl., ¶6.[3]

5. *CellPro will be permitted to continue commercial sales of its Ceprate® SC device pending FDA approval of Baxter's Isolex® 300 system or an alternative system licensed under the patents.*

As originally proposed, the stay of the injunction would not have encompassed additional infringing sales of the Ceprate® SC device to new customers, as distinguished from sales of disposable supplies to existing customers. Based on the information available to them, Hopkins and its licensees are confident that installations of CellPro's device and Baxter's device are now sufficiently widespread that patients already have broad access to stem cell separation technology.

---

[2] Copies of declarations and other papers referred to herein are included in the accompanying Appendix.

[3] CellPro's continued violation of FDA regulations could result in revocation of its limited approval for sales of the device.

However, CellPro's media campaign has raised fears among patients that this restriction might somehow deprive patients of care in the period prior to FDA approval of Baxter's system. In order to allay any possible concerns of this nature, Baxter has agreed to waive this restriction, and it has been removed from the current draft of the proposed order.

6. *CellPro's assertions that the royalty provisions of the proposed order would put it out of business are baseless.*

In their proposal to the court, plaintiffs requested that CellPro be required to pay them the amount of its incremental profit on future infringing sales of the Ceprate® SC disposable products. These items consist of reagents (including CD34 antibody), a disposable column and tubing. CellPro now sells these items for a package price of $4,325. CellPro's price reflects an 8% increase it put into effect immediately upon CellPro's learning of the FDA's grant of limited approval in December 1996.

CellPro has attempted to suggest that this condition of the stay is too onerous, and that it would remove any incentive to continue selling products. CellPro has not proposed any alternative royalty arrangement.

The question of what CellPro should have to pay on account of infringing sales is before the court, and it is premature to assume that plaintiffs' proposal will be adopted by the court. Nevertheless, based on the evidence, CellPro's arguments against the proposed payment are groundless.

CellPro complains that the proposed payment would cause it to lose money on every sale. This should not happen, because what plaintiffs seek by way of payment is only CellPro's incremental profit. In view of the fact that CellPro's sales constitute knowing and willful infringement of Hopkins' patents, it is difficult to see why CellPro should be rewarded for its wrongdoing by being permitted to retain the incremental profit on those sales. If CellPro does make profit, it will be able to use its revenues from infringing sales to support its other businesses and generally to enhance the value of the company for the benefit of its management and stockholders, all at the expense of Hopkins and its licensees. This seems fundamentally unfair.

In order to avoid "accounting games" in the calculation of incremental profit, plaintiffs suggested a minimum payment of $2,000 per sale, less than 50% of the selling price. CellPro argued in court that this was too high, asserting that the per unit "profit contribution" was only about $1,500. CellPro's calculation of the per unit incremental cost, in order to arrive at this figure, reflected exactly the sort of accounting games plaintiffs hoped to avoid. For example, in determining the per unit cost of disposables, CellPro included the total manufacturing cost of all Ceprate® SC related products, including the device itself, as opposed to the manufacturing cost

of the disposables alone. In addition, its per-unit cost figure is based on the total manufacturing and selling costs for all Ceprate® SC products over a 12-month period, even though CellPro only began selling Ceprate SC products in the U.S. in December. This obviously distorts the per unit profit substantially.

We do not propose that DHHS immerse itself in accounting issues; this is the job of the court, and if CellPro has demonstrated that plaintiffs' figure is too high, we presume that the court will make an appropriate adjustment. We raise the point here simply to show that CellPro's protestations of financial ruin are highly exaggerated and misleading.

Indeed, CellPro's assertion that having to pay plaintiffs its incremental profit on commercial sales will destroy its business was made without disclosure to DHHS of CellPro's actual financial condition. Since 1989, as a result of its development of stem cell separation products using the patented inventions, CellPro has been able to raise over $160 million from venture capitalists and in two public offerings. As of the end of 1996, it had $60 million in cash, the fruit of its unlawful infringement of Hopkins' patents. CellPro's cries of poverty are disingenuous.

There is no basis for CellPro's suggestion that payment of its incremental profit on sales will deprive it of any motivation to continue making product available to clinicians. First, in the case of clinical trials, plaintiffs do not seek to impose any minimum payment, and where CellPro provides free supplies to support the trial, plaintiffs have agreed to waive any royalty or other payment despite the infringement.

Second, the very fact that most of CellPro's activities in the area of stem cell separation are still directed to clinical trials shows that CellPro is fully prepared to supply products without making any incremental profit. In this case, if it is as responsible an institution as it claims to be, it should recognize that its own willful infringement and refusal to take a license when offered are what led to the predicament in which it finds itself. Presumably it wishes to support its hospital customers and maintain its reputation with clinicians. Under these circumstances, its threat to shut down sales of stem cell separation products if it has to pay plaintiffs its incremental profit on infringing sales is an irresponsible scare tactic that lacks any credibility.

Finally, CellPro's cell separation technology is not limited to use with the patented CD34 antibodies, and CellPro is well positioned to develop other cell separation products that do not infringe. Its own submissions describe its development of a T-cell depletion device, now being used in clinical trials, that uses T-cell antibodies not covered by Hopkins' patents. At the recent trial, CellPro's president, Richard Murdock, testified that the Ceprate® device could be utilized with a variety of different antibodies other than CD34, which would allow it to avoid infringement. Trial Tr. at 1098-99 (Exh. Q). CellPro is thus highly motivated to continue in

business and to service its customers responsibly during the period of transition from infringing products to noninfringing products. As MIT economics professor Jerry Hausman stated in support of the proposed order,

> CellPro has substantial business and market incentives to continue selling therapeutic disposables to the U.S. therapeutic market even if those sales make no contribution to R&D or to corporate overhead expenses. Companies with $50-$60 million in cash that find themselves blocked in one endeavor do not typically go out of business; rather, they seek to develop other, related products or services which build on the technological and human capital they have already developed, or they acquire new product lines or technology through purchase, licensing or joint venture. While this transition is taking place, however, CellPro has a very strong incentive to remain active and visible in the marketplace, developing and cementing relationships with researchers, customers and potential customers, as well as public awareness of the company. Consequently, provided CellPro does not suffer any direct, immediate loss as a result of each incremental sale (i.e., if its recovers its incremental cost), CellPro has a significant economic incentive to continue selling its therapeutic disposable products.

Hausman Decl. ¶ 14.

7. *CellPro's disparagement of Baxter's Isolex® 300 system and its prospects for FDA approval have no basis in fact.*

Citing § 203(a) of the Bayh-Dole Act, CellPro asserts that Baxter "has not taken, [and] is not expected to take within a reasonable time, effective steps to achieve practical application of" the patents to produce a stem cell separation system "capable of obtaining FDA approval." CellPro's statements about Baxter's Isolex® 300 system are factually incorrect, as it well knows. CellPro does not mention, for example, that Baxter's system received regulatory approval for sale throughout Europe in January 1995, more than two years ago, when it received the European CE Mark of Conformity for Medical Devices. This was *before* CellPro's device received European approval.

Within the United States, Baxter's Isolex® system has been installed in some 40 major transplant centers. These sites include, for example, Columbia Medical Center, Children's Memorial Hospital in Chicago, MD Anderson Cancer Center in Texas, Duke Medical Center, the New York Blood Center, UCLA Medical Center, Yale University School of Medicine, the Johns

Hopkins Hospital, and the Fred Hutchinson Cancer Research Center, the very institution in which CellPro's avidin-biotin cell separation technology was developed. Hauser Decl. ¶ 9. The Isolex® 300 system is also installed at the National Institutes of Health, where it is being used in a gene therapy clinical trial for treatment of Chronic Granulomatous Disease (CGD). The trial is being conducted by Dr. Harry Malech, Laboratory of Host Defenses, National Institute of Allergy and Infectious Disease. We encourage you to contact Dr. Malech about his experiences with the Baxter system (tel: (301) 480-6916).

The materials CellPro submitted to DHHS last week included several declarations from clinicians asserting that CellPro's Ceprate® SC system was superior to Baxter's system in terms of speed and ease of use. If true, these assertions at most would go to convenience; they would be irrelevant to the issue of public health. In any event, they are not true, and CellPro's submission was highly misleading. CellPro submitted, and presumably drafted, these statements knowing full well that they compare the CellPro system to the earlier generation Baxter product -- the 300 SA -- which was replaced by the 300i in 1996.

The Isolex 300i is an integrated and automated system, which relieves the technician of many of the manual steps that are still required in using CellPro's Ceprate® SC system. Using the 300i, a technician can complete the processing of blood or bone marrow in approximately 2.5 hours. The 300i provides high CD34+ purity and yields. Baxter's data shows that the 300i achieves median CD34+ purity of greater than 90%, allowing for tumor and T-cell depletion of up to 4 logs without sacrificing yield. We have enclosed for your information product literature and recent abstracts reporting clinicians' results using the Baxter system.

Baxter has also submitted declarations of several clinicians who have had personal experience with the Isolex® 300 system, including some who have used both Baxter's system and CellPro's system. Dr. Robert A. Preti, for example, has used both versions of the Isolex® system (the 300 SA and the automated 300i) in stem cell transplants at the New York Blood Center and the Hackensack Medical Center, including use of the system in four different FDA-approved clinical trials in which he is the Principal Investigator or Laboratory Investigator. He states:

> My experiences with the two Baxter devices have been entirely satisfactory. We have seen no delayed engraftment following any of the procedures. Yields and purities of CD34+ cells have been very good with the exception of one procedure that produced very high yield (82%) at the expense of relatively poor purity (77.8%). In recent trials using the 300i with breast cancer patients mobilized with chemotherapy, we have achieved CD34+ purities in the range of 95-99.5%.

Preti Decl. ¶4.[4]

Dr. James Vredenburgh, of Duke University Medical Center, has used both the 300 SA and the 300i in treatment of breast cancer patients. Vredenburgh Decl. ¶ 3. Duke Medical Center has performed more transplants in breast cancer patients than any other medical center in the world, and draws patients from all fifty states and foreign countries. He describes the 300i as "very easy to use." Id. ¶ 4. He adds that Duke Medical Center's experience with the Baxter devices

> has been very satisfactory. We have obtained high CD34+ purities and yields, and have not observed any toxicities associated with use of the device. Our patients have engrafted well, with no delays.

Id. ¶ 5. Although CellPro installed its Ceprate® SC system at Duke Medical Center, the Center uses Baxter's system in preference to CellPro's, and continued to do so even after CellPro received limited FDA approval for use of its product in autologous bone marrow transplantation. Id. ¶ 6.

Similar statements are made in declarations of Dr. Kenneth Carnetta, Dr. Bo Björkstrand, and Dr. Joan Garcia Lopez. Each of the declarants expects to continue using the Baxter product, notwithstanding CellPro's limited FDA approval in the United States and the availability of CellPro's SC system in Europe.

Dr. Preti has also used CellPro's Ceprate® SC device in transplant procedures. Based on his comparison of the SC and the 300i, his preference is for the Baxter device:

> In comparing the Isolex®300i with the CEPRATE® SC, I would say, first, that the overall processing time is virtually identical. The advantage of the Baxter device is that it is more fully automated than the CellPro device, which requires some additional manual operations that must be performed by a technician. This difference in automation frees up an additional 2 hours of technician time, during which the operator is able to perform other laboratory functions. Further, the Baxter device in our hands has more consistently provided high purities and recoveries of CD34+ cells. For these reasons, my preference is to use the Baxter device rather than the CellPro device in future procedures.

---

[4] By contrast, according to the testimony of CellPro's president, Richard Murdock, CellPro's Ceprate® SC device achieved CD34+ purity of only 40% in CellPro's Phase III clinical trial. Trial Tr. at 954 (Exh. Q).

Preti Decl. ¶ 5.

Dr. Björkstrand has also used both companies' products. In fact, his hospital is currently conducting a pilot program to compare the results of CellPro's® SC device and Baxter's Isolex® 300i in treatment of patients with neuroblastoma, acute lymphoblastic leukemia, multiple myeloma, and breast cancer. For each patient, the hospital processed one-half of the aspirated blood or bone marrow in the CellPro device and one-half in the Baxter device, and Dr. Björkstrand thereby compared the performance and capabilities of both systems. His conclusion:

> As far as ease of use, the Baxter system is more fully automated and easier to use than the CellPro system. As far as purity and yield of CD34+ cells, our experience has been that the Baxter system consistently provides higher purity and yield than the CellPro system.

Björkstrand Decl. ¶ 6. He adds that neither system has presented toxicity problems; as to CellPro's conjecture that the paramagnetic microspheres used in the Baxter system might be toxic to patients, he states that he has "no concern" in this regard. Id. at ¶ 7. Even though his hospital has used the CellPro system since 1992, his ultimate conclusion is that the Baxter system "gives us better results" and that "we expect to continue using the Baxter system in the future." Id. ¶ 8.

In its petition, CellPro also offers speculation about Baxter's prospects for FDA approval of the Isolex® system. It states that despite Baxter's greater resources, "it has been unable to obtain FDA approval for a stem cell separation system and may never do so."[5] It goes on to say, without attribution of source and without any supporting evidence, "we have been advised that no product other than CellPro's Ceprate SC is likely to be approved by the FDA in the foreseeable future." Petition at 7. These statements are baseless. As noted earlier, CellPro obtained FDA approval ahead of Baxter because it proceeded with product development in the face of Hopkins' patents, in contrast to Baxter, which did not begin product development until after obtaining a license under the patents.

So that the record is clear, plaintiffs have submitted the declaration of Baxter's Dr. Bonnie Mills, who addresses the FDA filing. CellPro's recent suggestion that the filing occurred hastily

---

[5]CellPro also states its "understanding" that Baxter "recently" began development of a product using a CD34 antibody other than My-10, and suggests that this change has "inevitably set back Baxter's efforts to obtain FDA approval." Petition at 7 n. 4. This statement is untrue and inexplicable. Baxter's Isolex® 300 system has always used a CD34 antibody other than My-10, as CellPro knows as a result of selling its Ceprate® SC system in competition with the Isolex® 300 system in Europe and elsewhere.

for purposes of litigation is preposterous in the circumstances: as Dr. Mills explains, the PMA submission consists of 56 volumes of text and data, amounting to some 20,000 pages of information. Baxter in fact made the decision to proceed with a PMA submission following a meeting with FDA officials in May, 1996, and originally hoped to file the PMA by the end of the year. Baxter delayed the filing in order to review with FDA staff, including an FDA statistician, the methodological approach which Baxter planned to use in analyzing the data supporting its PMA. In November 1996, the FDA accepted in principle Baxter's statistical model and its proposed use of data from a pivotal randomized breast cancer study as the basis for PMA approval. Baxter then proceeded with the data analysis and filed the PMA as soon as possible after completing the analysis and assembling the massive supporting information and data that underlay the submission. Mills Decl. ¶¶ 5-6.

CellPro's insinuation that the filing is of poor quality and unlikely to be accepted was made with no knowledge of the background of the submission or Baxter's extensive discussions with the FDA. Id. ¶ 5. Had the FDA agreed with CellPro's assessment of the filing, it could have rejected the filing as insufficient to permit substantive review. It did not. As Dr. Mills explains:

> Baxter's approach, involving extensive advance discussions with the FDA concerning Baxter's clinical data and its proposed statistical model for data analysis paid off earlier this month. By letter dated April 9, 1997, the FDA formally accepted Baxter's PMA submission as sufficient to permit substantive review as is, with February 24 as the filing date. As we understand it, the PMA will go through a review cycle of approximately six months. Consistent with this understanding, the FDA has advised Baxter that it will conduct a mid-cycle review meeting concerning Baxter's P.A. in May. We believe, based upon our informal discussions with FDA staff, that the PMA is on track for approval by the end of 1997.

Id. ¶ 7.

In the period following its negotiation of a license under the Hopkins patents, Baxter has invested tens of millions of dollars in research and development in support of its Isolex® 300 system. It has developed an outstanding stem cell selection system that is ready for FDA approval, and Baxter is hopeful that the FDA will move quickly to widen the availability of this system. But if the FDA does not, the public is protected, because under plaintiffs' proposal, the full force of any injunction will be stayed until after FDA approval.

II. Background of the Inventions and Steps Taken to Bring the Inventions to Practical Application.

In this part, we set forth in detail the background of the inventions, the steps taken to bring them to practical application, and CellPro's decision to willfully infringe the patents rather than to take a license, which would have assured its ability to make use of the technology in providing patient care and would have provided fair compensation to the patent holders. We also summarize why initiation of a march-in proceeding in these circumstances would be unwarranted and unwise.

The Patented Inventions

The inventions that are the subject of the patents in question were made at Hopkins in the early 1980s by Dr. Curt I. Civin. Since 1984, Dr. Civin has been Director of Pediatric Oncology at the Johns Hopkins Hospital. He is also Professor of Oncology and Pediatrics at the Johns Hopkins University.

The inventions provide a means by which scientists and clinicians can purify hematopoietic stem cells from the blood and bone marrow for use in research, diagnostics, and therapeutics, including stem cell transplantation. Stem cells are immature, undifferentiated cells that have the capacity to divide and proliferate in order to produce all the different types of myeloid and lymphoid cells that make up the blood and immune systems. Stem cells are extremely rare, and prior to Dr. Civin's work, there was no effective way to isolate them or even identify them.[6] One of the patented inventions (the '204 patent) covers monoclonal antibodies that recognize a unique antigen discovered by Dr. Civin that is expressed on the surface of stem cells and is not detectable on mature cells of the blood and bone marrow. That antigen is now known in the scientific community as the "CD34" antigen, and monoclonal antibodies that bind to that antigen are known as "CD34 antibodies." The other invention (the '680 patent) covers suspensions of highly purified stem cells that are substantially free of mature myeloid and lymphoid cells. Using the CD34 antibodies of the '204 patent in combination with known cell separation techniques enables doctors to obtain the purified stem cell suspensions of the '680 patent.

NIH Funding

In an effort to discover novel and useful leukocyte differentiation antigens, Dr. Civin began focusing his research on the development of new monoclonal antibodies in the 1979-80 time frame. In October 1979, prior to his discovery of the CD34 antigen, Dr. Civin applied for an

---

[6]In accordance with conventional terminology, the term "stem cells" is used herein to encompass all CD34+ lympho-hematopoietic stem cells and progenitor cells.

NIH research grant (Application No. 1 R01 AI17136-01) to study "Identification of Human Mono-myeloid Cell Surface Antigens." This application was *denied*.[7]

Dr. Civin proceeded with his research nevertheless. He made the hybridoma cell line producing the first monoclonal antibodies to the CD34 antigen (which he initially named "My-10" but since has been renamed "CD34") in May 1981. In June 1981, Dr. Civin applied for an NIH research grant to support his continuing work, including additional testing of the antibodies he had previously made. In 1982, his proposal was accepted (although the amount of funding was reduced) by the award of a three-year grant commencing May 1, 1982 (No. 1 R01 CA 32318-01). The grant thus began approximately one year after Dr. Civin made the hybridoma that produced CD34 monoclonal antibodies. The 1982 grant letter did not incorporate the march-in provisions of the Bayh-Dole Act, and the award was not made subject to those provisions.

Award of the Patents to Hopkins

Under Hopkins' policy on patent rights, Dr. Civin's inventions were assigned to Hopkins, which applied for patent protection on February 6, 1984. The Patent and Trademark Office ("PTO") determined that the application encompassed four separate inventions, and directed that they be prosecuted one at a time. The PTO eventually issued four patents. The two patents currently involved in the CellPro litigation are U.S. Patent No. 4,714,680 (the '680 patent) and U.S. Patent No. 4,965,204 (the '204 patent). The '680 patent issued in 1987; the '204 patent issued in 1990. The '204 patent covers all monoclonal antibodies that specifically bind to the CD34 antigen. The '680 patent covers suspensions of human cells that contain stem cells and are substantially free of mature cells.

The third and fourth patents to issue were U.S. Patent No. 5,035,994 (the '994 patent) and U.S. Patent No. 5,130,144 (the '144 patent). These patents issued in 1991 and 1992, respectively. The '994 patent claims a method of separating stem cells using CD34 monoclonal antibodies, and the '144 patent claims a method of using purified stem cell suspensions in bone marrow transplantation.

In 1994, in response to CellPro's attack on the patents, Hopkins asked the PTO to reexamine the '680, '994 and '144 patents in light of the prior act cited by CellPro. In each case, the PTO reaffirmed the patentability of the claimed inventions. In 1996, in order to simplify the

---

[7]During this period, the only NIH funding to which Dr. Civin had access was the NIH Regional Oncology Center CORE Grant to JHU (No. CA 06973-19), which provided partial salary and laboratory support to a number of junior investigators at Hopkins, including Dr. Civin. This grant preceded the Bayh-Dole Act and was not directed toward any particular research or development.

issues for the jury, Hopkins, Becton and Baxter elected not to pursue claims against CellPro under the '994 and '144 patents. The jury's recent determination of willful infringement covered both patents (the '680 patent and the '204 patent) that remained in the case.

Steps Taken By Hopkins to Achieve Practical Application of the Inventions

In 1984, at the same time it applied for patent protection, Hopkins initiated steps to ensure that Dr. Civin's inventions would achieve practical application and be made available for the benefit of the public. Through the Office of Technology Licensing at the Hopkins School of Medicine, Hopkins negotiated an exclusive worldwide license agreement with Becton, a prominent commercial supplier of monoclonal antibodies and medical devices based in New Jersey. Under the agreement, Becton obtained an exclusive license under the patents which thereafter issued to Hopkins based upon Dr. Civin's work. The agreement obligated Becton to pursue diligently the development of products for research, diagnostics and therapeutics, and also gave Becton the right to grant sublicenses under the patents.

Becton promptly developed a commercial reagent containing CD34 antibodies derived from Dr. Civin's original hybridoma cell line, which it began selling in 1985. Over the past twelve years, Becton has successfully sold CD34 antibodies derived from that hybridoma as well as CD34 antibodies derived from another CD34 hybridoma made some years later by another laboratory following Dr. Civin's teachings. Becton's commercialization of CD34 antibodies assisted scientists throughout the world to study the function and characteristics of the CD34 antigen, an important predicate to clinical use of CD34 antibodies in transplantation therapy. (Since 1984, more than 2,300 scientific papers citing the CD34 antigen have been published.) Becton has also developed a diagnostic kit for counting CD34 positive cells in blood and bone marrow. That kit is awaiting FDA approval for sale in the United States.

Although Becton originally planned to develop a therapeutic product as well, in the late 1980s it made a corporate decision not to enter the therapeutic market. It promptly undertook a search for another company having the resources and experience that would be needed to commercialize Dr. Civin's inventions in the therapeutic field. In 1990 (prior to issuance of the '204 patent), it sublicensed exclusive rights in the fields of therapeutics and therapeutic research to Baxter. Baxter is a global medical products and services company based in Illinois with particular expertise in technologies relating to the blood and circulatory system.

As discussed in Part I, Baxter proceeded to develop a therapeutic device, the Isolex® 300 system, which utilizes the patented inventions to provide highly purified stem cell suspensions for

use in bone marrow transplantation and other therapies.[8] The Baxter system is in use today in FDA-approved clinical trials in major transplant centers located throughout the United States. (A list of U.S. sites at which the Baxter system is installed is included in the Declaration of Kristin Hauser, ¶ 9.) In February, Baxter submitted its premarket approval application ("PMA") to the FDA for approval to begin sales of the product in the United States, and the FDA has notified Baxter of its acceptance of the PMA filing as sufficient to proceed with the review and approval process. To date, more than 800 patients worldwide have participated in clinical trials using the Isolex® 300 system. Baxter's system received regulatory approval in Europe in January 1995 and is currently being sold there. It has exclusive status as an Orphan Device in Japan and recently completed clinical trials for regulatory submission in Japan. The system has also received regulatory approvals for product sales in a number of other countries, including Argentina, Hong Kong, Israel, New Zealand and Singapore.

CellPro's Development of Infringing Products

CellPro was formed in March 1989 by Dr. Ronald Berenson, who was formerly associated with the Fred Hutchinson Cancer Research Center ("FHCRC"). In the mid-1980s, some four years after Dr. Civin's discovery of the CD34 antigen, scientists at FHCRC had made another CD34-antibody-producing hybridoma, which they called "12.8." In the litigation, the court found that the 12.8 hybridoma was made by FHCRC by following Dr. Civin's published teachings. Johns Hopkins University v. CellPro, 931 F. Supp. 303, 323 (D. Del. 1996) (Exh. J). Dr. Berenson evidently had experience with the 12.8 antibody at FHCRC, and when he formed CellPro in 1989, he arranged to obtain a license from FHCRC permitting CellPro to use the 12.8 hybridoma as a source of CD34 antibodies.

At the time CellPro was formed, its management was aware of the issuance of the '680 patent to Hopkins, which covers purified suspensions of stem cells. CellPro nevertheless focused its product development activities on the manufacture of a stem cell concentrator device designed to produce stem cell suspensions substantially free of mature cells, exactly what the '680 patent claims. CellPro was also aware from the outset that Hopkins had pending claims under consideration by the PTO that, if allowed, would give it exclusive patent rights to all CD34 antibodies, including the 12.8 antibody that CellPro had obtained from FHCRC. CellPro nevertheless proceeded to develop its device using the 12.8 antibody to identify and purify stem cells.

---

[8]Baxter also developed a cell separation device, the Isolex® 50 Magnetic Cell Separation System, that uses the patented CD34 antibodies to purify stem cells for therapeutic research purposes. This product is currently available for sale in the United States and does not require FDA approval.

When the '204 patent issued to Hopkins in October 1990, CellPro continued its product development activities unabated. Its IDE submitted to the FDA in December 1990 to obtain authorization for clinical trials described its product as utilizing antibodies specific to the CD34 antigen in order to produce purified suspensions of stem cells. CellPro did not seek or obtain any opinion of patent counsel with respect to the '204 patent for months after its issuance, and when CellPro finally obtained an opinion in April 1991, the opinion made clear that the '204 patent covered all monoclonal antibodies to the CD34 antigen and thus covered the 12.8 antibody. In short, CellPro knew of both the '680 and the '204 patents, knew that its products infringed them, and yet proceeded to develop and sell its infringing products nevertheless.

At the recent trial, CellPro contended that it proceeded with the development of its stem cell concentrator products based upon opinions of counsel that the Hopkins patents were invalid and unenforceable. The district court has ruled, as a matter of law, that the patents are both valid and enforceable. The jury's finding of willful infringement, moreover, represented a determination that CellPro could not reasonably have relied upon the opinions of counsel it cited, and that it had no good faith basis for asserting the invalidity and unenforceability of the patents.

CellPro's Refusal to Take a License Under the Patents

In January 1992, Baxter made a decision to offer sublicenses under the Hopkins patents to other United States companies that appeared to be interested in developing therapeutic products using the patented inventions. These companies included Systemics, Inc., Applied Immune Sciences, Inc. and CellPro. Baxter sent substantially identical letters to each of these three companies indicating the principal terms on which it was willing to license. It had discussions with all three companies.

Of the three companies Baxter approached, CellPro was the only one that did not take a license on the terms offered by Baxter. CellPro instead proposed royalty terms so favorable to CellPro that, had such terms been accepted by Baxter, Baxter would have had to pay its licensor (Becton) more money on account of each CellPro sale than Baxter would have received from CellPro with respect to that same sale. Baxter declined to grant CellPro a license on these terms.

In April 1992, rather than continue negotiations, CellPro sued both Baxter and Becton in federal district court in Washington, requesting a declaratory judgment that the patents were invalid and unenforceable and that CellPro did not infringe them. That case was dismissed on jurisdictional grounds.

In July 1992, despite CellPro's unwarranted initiation of litigation in Washington, Baxter wrote to CellPro and renewed its offer for a license, on the same terms it offered CellPro in

January of that year. The parties met in August, at which time Baxter repeated the offer. CellPro again turned it down.

In March 1994, in the face of CellPro's continued infringement and refusal to take a license, Hopkins, Becton and Baxter sued CellPro for patent infringement in federal court in Delaware.

The Patent Infringement Litigation Against CellPro

The Delaware suit first went to trial in July 1995. After CellPro presented all its evidence, plaintiffs moved for judgment as a matter of law, on the ground that the evidence would not support a verdict in favor of CellPro. The court did not act on plaintiffs' motion during trial, reserving it for decision post-verdict. The jury then found for CellPro.

After the jury verdict, plaintiffs renewed their motion, and, in the alternative, requested a new trial, on the ground that the verdicts were contrary to the evidence, legally inconsistent and the product of jury confusion. In June 1996, the court granted plaintiffs judgment as a matter of law that CellPro's products infringed two of the patents, and ordered a new trial as to CellPro's other defenses. The new trial order was entered following the court's comprehensive review of the case, which showed that the evidence overwhelmingly supported plaintiffs. See Exh. J.

In further proceedings in 1996 and 1997, the court again considered CellPro's invalidity and noninfringement defenses. After analyzing the additional evidence CellPro proposed to offer in the new trial, the court ruled that plaintiffs were entitled to summary judgment as to each of CellPro's defenses, concluding that no reasonable jury could fail to find that the patents are valid and that CellPro infringes them. The case then proceeded to trial before a jury commencing on March 4, 1997. (Unbeknownst to plaintiffs, CellPro filed its petition with DHHS one day earlier).

At the recent trial, the jury was asked not only to determine damages to compensate for CellPro's past infringement, but also to evaluate CellPro's conduct, in order to determine whether CellPro's decision to proceed with the development and marketing of its stem cell selection products in the face of the patents had any good faith, reasonable basis. The jury found that plaintiffs had proven, by clear and convincing evidence, that CellPro willfully infringed both the '680 and the '204 patents -- i.e., that it knew of the patents and had no good faith basis to believe it had a legal right to engage in its infringing activities. The jury also awarded compensatory damages of $2.3 million, based upon CellPro's infringing sales to date. Shortly after the finding, the court also ruled against CellPro on its allegation that the patents were unenforceable based upon alleged inequitable conduct in the PTO by Hopkins.

On April 30, 1997, the court heard oral argument on three post-trial motions filed by plaintiffs. The first two ask the court to award treble damages and attorneys' fees under 35 U.S.C. §§ 284 and 285 in light of the jury's finding of willful infringement. The third motion seeks equitable relief to remedy CellPro's past infringement and prevent future infringement, subject to a partial stay pending FDA approval of Baxter's Isolex® 300 system, as discussed in Part I. At the hearing, the court determined that it should resolve another pending issue in the case prior to considering the scope of any equitable relief. Plaintiffs currently expect that it will be well into June or July before the court acts on the motion for equitable relief.

Timing and Scope of Equitable Relief

CellPro's petition is in a very real sense premature, because the court has not yet imposed any restrictions on CellPro's continued sales of its Ceprate® SC system, and CellPro has filed papers with the court asking that, in the exercise of its equitable discretion, it not do so. Moreover, plaintiffs' proposed stay of any injunction will alleviate any public health concerns.

As discussed in Part I, in order to minimize any disruption to patients being treated using CellPro's therapeutic device, and to ensure a smooth transition to Baxter's Isolex® 300 system, Hopkins and its licensees proposed a transitional period, during which the injunction will take effect in stages. Under the proposed transition, CellPro would be allowed to continue selling the Ceprate® SC device and CD34 antibodies and other disposables used with the device to customers in the United States until the FDA approves Baxter's system (or an alternative system licensed under the patents) for sale in the U.S. It would also be allowed to continue sponsoring and supporting FDA- and IRB-approved clinical trials using the Ceprate® SC system. Outside the United States, where both the Baxter system and the CellPro system have received regulatory approval and are sold commercially, the injunction would allow CellPro a 12-month period to phase down sales of its product. (We have not addressed the details of the proposed order as it affects sales outside the United States, which we do not understand to be a matter within DHHS's jurisdiction.) Plaintiffs' intent is that the court fashion an equitable decree that will protect the legal rights of Hopkins and its licensees while assuring that there is no gap whatsoever in providing treatment to patients in need of stem cell transplants using the patented technology.

A copy of the current draft of the proposed injunction is included in the Appendix as Exh. I. We emphasize that the court has not entered an order in this or any other form, and that it is likely to go through further revisions before it takes effect in any form.

Summary of Reasons to Deny CellPro's Petition

There are a number of reasons why DHHS should decline to initiate a march-in proceeding. First, Hopkins took prompt and effective steps to bring Dr. Civin's inventions to

practical application. The same year it applied for patent protection, it licensed out the technology to Becton, a substantial and well-qualified licensee. Within a year, Becton made CD34 antibodies available commercially, and scientists were able to begin using them in the laboratory to develop necessary data, including the characteristics of the antigen, the specificity and utility of CD34 antibodies, and the specific characteristics of CD34+ cells. Becton also proceeded to develop a diagnostic kit that enables clinicians to determine the CD34 positive cell count of patients undergoing transplantation procedures. In 1996 Becton submitted an application to the FDA for approval of commercial sales of the kit in the United States.

In the therapeutic field, Becton provided sponsorship to Dr. Civin, who undertook a clinical trial to investigate the use of highly purified stem cells to replace damaged stem cells of patients who had undergone high dose chemotherapy. Ultimately, Becton decided not to enter the therapeutic market with its own product, but when it made that decision, it promptly identified other qualified companies and sublicensed its rights in this field to Baxter in August 1990. Baxter thereafter invested tens of millions of dollars in developing the Isolex® 300 system, which is now on sale in many countries of the world, is widely used in FDA-approved clinical trials in the United States, and is awaiting FDA approval.

Second, there are no health or safety needs that necessitate action by DHHS. Baxter's system is available for use under FDA-approved IDE's in clinical trials in major transplant centers throughout the United States, including FHCRC, the institution where CellPro's device originated. CellPro's device has only just recently (in December 1996) received FDA approval. Moreover, CellPro's device is approved only for use in autologous bone marrow transplantation; CellPro does not have approval for use of its device in selection of stem cells from peripheral blood, which represents the most common source of stem cells for transplants performed today. As to these uses of the CellPro system, CellPro has yet to demonstrate to the FDA that its system is safe and effective, and unlike Baxter, it has not even applied for FDA approval to use the system in this way.

In any event, the proposed injunction against infringing sales of the CellPro device would not take effect in the United States until after Baxter receives FDA approval for sales of its Isolex® 300 system, and would permit CellPro to continue to completion all current clinical trials and all future clinical trials approved on or before the date Baxter receives FDA approval. Under these circumstances, there can be no justification for DHHS's taking the extraordinary and unprecedented step of overriding a nonprofit institution's licensing program to grant a compulsory license to another party.

Finally, a decision to initiate a march-in proceeding in the circumstances of this case would have a profoundly negative impact on the ability of Hopkins and other nonprofit medical institutions to achieve practical application of inventions in biotechnology and other areas of

medical technology through patent licensing programs, which is the very purpose underlying the Bayh-Dole Act. CellPro's argument for a compulsory license is based on the fact that, as of today, it alone has received FDA approval for limited use of its therapeutic device for concentrating stem cells utilizing CD34 antibodies. The *reason* that it alone has received FDA approval is simple. CellPro helped itself to a head start in product development by disregarding Hopkins's patent rights. Baxter, by contrast, did not commence its product development until after it obtained a license under the patents, approximately a year-and-a-half after CellPro began its development efforts. Granting a compulsory license to CellPro under the Bayh-Dole Act thus would reward CellPro for its willful infringement.

Baxter's development of a successful therapeutic product has entailed substantial investments, including payment of an up-front license fee of $1.25 million in 1990, tens of millions of dollars in research and development expenses, support for clinical trials, and massive regulatory submissions. To attract private investment on this scale, nonprofit institutions must be able to offer their licensees the protections and incentives afforded by the patent system. If a company like CellPro can flaunt the licensing process, willfully infringe the patents, force the expenditure of millions of dollars in legal expenses by licensees who acted in good faith by respecting the patents and then, when faced with the consequences of its misconduct, obtain a compulsory patent license from DHHS, the value of patent rights in the hands of nonprofit institutions like Hopkins will be significantly diminished. Indeed, if CellPro succeeds here, it is hard to see why any private company would feel compelled to negotiate a license under patents for medical technology where government funding is involved: if it challenges the patents and wins, it avoids paying any royalties, and if it challenges the patents and loses, it can simply turn to DHHS for a compulsory license. Hopkins urges DHHS not to permit the Bayh-Dole Act to be so cynically manipulated by a company like CellPro after it has been found to be a willful infringer.[9]

---

[9]Hopkins' objective here is to remove any concern on the part of DHHS that initiation of a march-in proceeding is needed. Hopkins notes, however, that there remains a serious issue as to whether DHHS would have any jurisdiction under the Bayh-Dole Act to do so, and by submitting this response, Hopkins does not waive, and expressly reserves, its tentative conclusion that DHHS lacks jurisdiction. Although the '680 patent makes reference to NIH support, Dr. Civin in fact made the first monoclonal antibodies to the CD34 antigen in May 1981, prior to NIH's award of a research grant in 1982. The grant he received in 1982 did not incorporate the Bayh-Dole march-in procedures in its terms, and it was not made subject to government march-in rights. While Dr. Civin had the benefit of NIH funding after 1982 to continue his studies of the CD34 antigen and to investigate in further detail the utility of CD34 antibodies, it does not follow as a legal matter that the patented inventions are subject to the march-in provisions of the Bayh-Dole Act.

III. CellPro's Petition Distorts the Facts.

CellPro's petition offers no legitimate grounds for intervention by DHHS on its behalf. It also grossly distorts the facts. We address here only a partial list of its misstatements.

1. Background of Dr. Civin's inventions. CellPro implies in its discussion of the background of the inventions that Dr. Civin merely followed the teachings of Drs. Koeffler and Golde to produce CD34 antibodies. CellPro made this same argument in federal court in support of its obviousness defense, and the court firmly rejected it. Drs. Koeffler and Golde did not study normal hematopoietic cells and did not make monoclonal antibodies. We are unaware of any scientist who credits Drs. Koeffler and Golde with discovery of the CD34 antigen.

CellPro suggests that Dr. Civin merely "discovered a monoclonal antibody," which he named "My-10," and that FHCRC thereafter "discovered a monoclonal antibody they called 12.8." Petition at 3. Monoclonal antibodies are not "discovered," they are made, and it was Dr. Civin who taught the scientists at FHCRC and elsewhere how to make CD34 monoclonal antibodies after his discovery of the previously unknown CD34 antigen . The CD34 antigen was the first and only antigen shown to be expressed on the surface of stem cells and not to be detectable on mature cells, thus providing scientists for the first time an effective marker to identify and separate stem cells from mature myeloid and lymphoid cells. Dr. Civin's subsequent publications disclosing the characteristics of the antigen and his method for making monoclonal antibodies reactive with that antigen enabled other scientists skilled in the art to make additional CD34 antibodies, all of which can be used, in combination with known separation techniques, to separate the cells that express the CD34 antigen.

2. The 12.8 hybridoma and CellPro's infringing products. The 12.8 hybridoma, which produces the CD34 antibodies utilized in CellPro's products, was made by FHCRC four years after Dr. Civin's pioneering work. As the court found, FHCRC made the hybridoma by following the methodology taught by Dr. Civin in his publications. The 12.8 antibody is one of more than 50 different CD34 antibodies that have been made since Dr. Civin disclosed the method for doing so, all of which share the ability to bind specifically to the CD34 antigen and thereby identify stem cells.

CellPro's statement that the 12.8 antibody differs because it "binds in 10 places rather than two as does My-10" is misleading. This statement merely refers to the fact that the 12.8 antibody is an IgM class immunoglobulin and therefore each molecule has ten potential antigen binding sites, whereas My-10 is an IgG class immunoglobulin and therefore each molecule has two potential antigen binding sites. Each of these antibodies nevertheless binds specifically, and only, to the CD34 antigen. As CellPro knows but fails to acknowledge, the My-10 antibody is a

commercially available CD34 antibody (sold by Becton under the trade name "HPCA-1") and it has been used successfully at Hopkins in bone marrow transplantation.

CellPro correctly states that FHCRC granted a license to CellPro to use the 12.8 antibody in its products. This was a hybridoma license, not a patent license, merely giving CellPro the right to use FHCRC's 12.8 hybridoma cell line as the source for CD34 antibodies. FHCRC did not apply for (and could not have obtained) a patent on CD34 antibodies, and this case presents no conflicting claims to patented technology. Indeed, in 1991, after issuance of the '204 patent to Hopkins, FHCRC and CellPro renegotiated their hybridoma license, and CellPro expressly agreed to indemnify FHCRC for patent infringement claims made against FHCRC on account of CellPro's use of the 12.8 antibody.

CellPro's statement that the FDA approved its Ceprate® SC system for use in the United States in December 1996 is only partly true. The FDA's approval of the system was limited to use in autologous (self) bone marrow transplantation. See Exh. O. The CellPro device is not approved for use in allogeneic (donor) transplants, and it is not approved for use in peripheral blood stem cell transplantation. As noted earlier, 85% or more of transplants performed today use peripheral blood as the source of stem cells, and CellPro is not permitted under FDA regulations to sell its device for that purpose.

3. Baxter's Isolex® 300 system. CellPro's misstatements with respect to Baxter's Isolex® 300 system run throughout CellPro's petition and are rebutted in Part I.

4. The Hopkins patents. CellPro's discussion of the scope of the '204 patent is disingenuous. It says that the patent is "now claimed" to cover CD34 antibodies other than the original My-10 antibody (Petition at 15; see Petition at 5), as if CellPro were the victim of a recently contrived interpretation of the patent. In fact, claim 1 of the patent was expressly written to cover all monoclonal antibodies that bind to the antigen; only claim 3, which depended on claim 1, was limited to the specific My-10 antibody manufactured in Dr. Civin's laboratory.

The federal court's construction of claim 1 to cover all CD34 antibodies could not have been a surprise to CellPro. CellPro's petition fails to disclose that in 1991 it received an opinion of outside patent counsel — the same outside counsel that represented it in the litigation — construing the patent in exactly the same way it was construed by Judge McKelvie. CellPro and its patent counsel have known all along that the '204 patent covers all CD34 antibodies, including the 12.8 antibody, as the jury found when it rendered its verdict of willful infringement.

CellPro also knows that construing the '204 patent to limit protection to the original My-10 hybridoma and antibody would render the patent meaningless. Every monoclonal antibody, including every CD34 antibody, is slightly different from every other monoclonal antibody. Once

Dr. Civin disclosed the method for making CD34 antibodies, other scientists could make copies simply by following his teachings; for that reason, the Patent Office recognizes that meaningful patent protection must encompass all antibodies to the same antigen.

CellPro's discussion of the '680 patent is equally misleading. The petition feigns surprise that a patent could be construed to encompass human stem cell suspensions regardless of "how those suspensions are created." Petition at 5 & n.4. In fact, product claims such as this are commonplace, particularly where, as here, the purity of the composition was previously unattainable. Furthermore, it is black letter patent law that product claims are valid as long as the patent teaches at least one method of making the product. See Johns Hopkins, 931 F. Supp. at 323 (Exh. J).

In considering CellPro's comments on the scope of the claims, DHHS should bear in mind that when the jury evaluated CellPro's assertions, it concluded, unanimously, that they were not made in good faith.

5. Small business preference. CellPro asserts that when Becton decided in 1989 to withdraw from the therapeutic market, Hopkins should have given a preference to CellPro for a license under the patents in therapeutic field. Petition at 6. This argument is a red herring with no factual or legal basis. It is a red herring because CellPro had only just been formed in 1989. In an expert report filed in connection with the recent trial, CellPro claimed that it could not even have afforded a $750,000 up-front license fee as of the fall of 1990. Assuming that to be true, it scarcely could have presented itself in 1989 as a company having the capability and resources required to bring the patented inventions to practical application in the therapeutic field.

Furthermore, as a legal matter, 37 C.F.R. § 401.14(k)(4) applies only where the prospective licensor is a nonprofit organization. In this case, Hopkins had conveyed exclusive rights to Becton in 1984, including the right to grant sublicenses, and Becton was not subject to the regulation. Hopkins's grant of exclusive rights to Becton in 1984 (long before CellPro even existed) was entirely consistent with the provisions of the Bayh-Dole Act, and there is nothing in the Act that gave Hopkins the authority to terminate Becton's license in 1989 in order to offer a license to CellPro.

Finally, CellPro's quotation from § 401.14(k)(4) is misleading. It omits the very next sentence of the regulation, which states "The decision whether to give a preference in any specific case will be at the discretion of the contractor." This regulation provides no basis whatsoever for initiation of a march-in proceeding.[10]

---

[10]Section 401.7(b) of the regulations provides that a small business firm that believes a

(continued...)

In its petition, CellPro attempts to blame its failure to obtain a license in 1992 on Baxter's alleged demand for exclusive distribution rights to CellPro's product in Europe. Petition at 9. CellPro's presentation of the facts is incomplete and misleading. At trial, the evidence (including the internal notes of CellPro's president at the time) showed that at that time CellPro in fact was looking for a corporate partner to act as its exclusive European distributor, and that it initiated discussions with Baxter for that purpose. Tr. 1288-89 (Exh. Q). In April 1992 Baxter made a proposal that included European distribution because it believed CellPro was interested in such a proposal, and in making that proposal Baxter also offered to reduce significantly the royalty rate and up-front obligation in exchange. In appending to its petition a selection of correspondence between CellPro and Baxter from "early in 1992," CellPro omits Baxter's July 22, 1992 letter. In that letter, Baxter expressed its surprise at CellPro's reaction to its April proposal, given CellPro's earlier indications of interest in a distribution arrangement with Baxter, and *reiterated* its willingness to license CellPro on the terms originally proposed, with no distribution rights included. See Exh. K.

Two pages later, CellPro's petition acknowledges, begrudgingly, that Baxter again made its original offer available to CellPro. Petition at 11. It then states that CellPro "later offered to accept that proposal." This statement is made without any documentation to support it, and it is a flat-out misrepresentation of fact. Included in our Appendix as Exh. L is a letter dated January 15, 1993 from CellPro's counsel to Baxter's counsel.[13] In it, he states:

> On August 27, 1992, CellPro, at Baxter's request, traveled to Baxter offices in Chicago and held face-to-face settlement discussions. At these discussions, Baxter repeated its July 22, 1992 proposal and CellPro unequivocally rejected it.

In 1994, at the suggestion of Hopkins, Baxter and Becton Dickinson, the parties participated in voluntary mediation, during which Baxter again offered CellPro a license under the patents, which CellPro rejected. By agreement of the parties, the mediation was conducted under a stipulation of confidentiality, and CellPro' summary of positions taken during the mediation and in the course of subsequent settlement negotiations is inaccurate, misleading and in violation of its agreement of confidentiality.

---

[13]CellPro' letter was sent in response to the declaration of a Baxter attorney pointing out that CellPro had never officially responded to the license offer that was made in Baxter's July 22, 1992 letter.

6. Baxter's offer to license the patents in 1992. CellPro concedes, as it must, that it was afforded the opportunity in 1992 to take a license under the Hopkins patents and turned it down. As noted earlier, CellPro was the only company to do so, and it has only itself to blame for the predicament in which it finds itself today.

As CellPro acknowledges, when offered a license by Baxter, it rejected Baxter's proposal and insisted on financial terms far more favorable to it than those accepted by Systemics and Applied Immune Sciences ("AIS"). Whereas Systemics and AIS each paid Baxter a $750,000 non-refundable up-front fee,[11] CellPro was willing only to pay a $500,000 advance to be credited against future royalties. In the recent trial, the jury determined that, as of October 1990, a reasonable licensee in CellPro's position would have been willing to pay Baxter a $1 million non-refundable license fee.

Systemics and AIS also agreed to pay a running royalty amounting to 8% of net sales of products utilizing a CD34 antibody.[12] The jury determined that a reasonable licensee in 1990 in fact would have been willing to pay Baxter a 10% royalty on net sales of such products. In 1992, however, CellPro demanded a much reduced royalty that would be applied to only a portion of its net sales, based upon the ratio of the manufacturing cost of the antibody component of the product to the total manufacturing cost of the product, even though monoclonal antibodies are much less expensive to manufacture than the other components of a stem cell concentration device. According to Mr. Murdock's testimony at trial, under CellPro's proposal, this calculation would have resulted in a royalty rate of approximately 3.2%, far less than the royalty Baxter would have been required to pay Becton on account of each CellPro sale. Trial Tr. at 1102-03 (Exh. Q). CellPro's chief negotiator at the time, Thomas Kiley, confirmed in his testimony at trial that Mr. Murdock's proposal to Baxter represented CellPro's "final offer". Id at 1373.

(...continued)
nonprofit organization is not meeting its obligations with respect to small business preferences may report its concerns to the Secretary of Commerce. If CellPro had truly believed in 1990 that Hopkins was failing to meet its obligations, it could have sought assistance from the Department of Commerce. As far as we are aware, it did not.

[11]Systemics in fact agreed to pay Baxter a $1 million up-front fee. Subsequently, Baxter agreed to credit Systemics for the last $250,000 of the fee based upon Systemics' agreement to purchase products from Baxter.

[12]In the licenses, the nominal royalty rate was 16%, but the royalty base was only 50% of net sales. The effective royalty rate thus was 8%.

Because Hopkins was a participant in the discussions, it can say with confidence that at no time did CellPro ever offer to accept Baxter' license proposal.[14] CellPro elected instead to disregard the patents, to proceed with the development and marketing of infringing products, and to initiate vexatious litigation in an ill-considered effort to invalidate the patents. It took this course, the jury found, having no good faith basis for believing the patents were invalid, unenforceable, or not infringed.

7. CellPro's discussion of "reasonable" license terms. For the reasons previously stated, there is no basis for DHHS to initiate a march-in proceeding, and thus there is no reason to respond specifically to CellPro's discussion of what it claims would be "reasonable" terms for a compulsory license to CellPro. We note, however, that many of the same arguments made in CellPro's petition were also presented to the jury in Delaware. The jury emphatically rejected CellPro's arguments, and found that a reasonable royalty for a license negotiated in 1990 would have included a nonrefundable up-front fee of $1 million and a running royalty equal to 10% of CellPro's net sales of its stem cell concentrator devices. Today, nearly seven years later, it would be reasonable to expect that the up-front and royalty terms of a license coming from Baxter would be materially different. In 1990, Baxter had not even begun to develop a product; as of today, it has invested tens of millions of dollars in a product that is on sale in Europe and other countries and is ready for FDA approval in the United States. Moreover, the validity of the patents has been confirmed both by the PTO in the reexamination proceedings and by the federal court in the litigation, and the parties have spent millions of dollars defending the patents against CellPro's bad faith and vexatious attack. It would be unreasonable to expect a license in 1997 to be offered by a reasonable licensor on the same terms that might have been negotiated in 1990 or 1992.[15]

---

[14]At page 16 of the petition, and in footnote 13, CellPro represents that in March 1994 it "indicated to Baxter it was willing to pay" the royalty proposed by Baxter in 1992. Once again CellPro offers no documentation to support this claim. In March 1994, CellPro did write to Baxter inquiring as to whether Baxter's 1992 offer was still on the table (Exh. M). Nowhere in that letter did CellPro state its willingness to pay the royalty proposed by Baxter if the answer to the inquiry were in the affirmative. In reply, Baxter wrote that if CellPro were interested, it was willing to reopen license negotiations with the assistance of the mediator. Exh. N. CellPro did not respond.

[15]CellPro's ostensible concern about the impact of third-party royalty payments on the cost of medical care is hypocritical. As soon as CellPro received FDA approval for sales in the United States, it increased the price of the disposable supplies from $4,000 to $4,325, an 8% hike. At the trial, CellPro's former director Thomas Kiley complained about Baxter's pricing in Europe because Baxter was *underpricing* CellPro in the market. Trial Tr. at 1360 (Exh. Q).

8. CellPro's insistence that DHHS march in ahead of the court. CellPro filed its petition even before the trial in March, without awaiting any judicial determination as to the appropriate scope and timing of an injunction. This makes no sense. Until the court decides whether and to what extent equitable relief should be entered, CellPro's petition is premature and should be denied. Under federal law, the court will take account of the public interest in fashioning any injunctive relief, and CellPro has argued against the proposed order on public interest grounds. DHHS's initiation of a proceeding at this time would not give the court an opportunity to consider the merits of CellPro's arguments, which, if meritorious, may moot the entire issue.

CellPro's anxiety about uncertainty in the minds of its investors is revealing, but should be of no concern to DHHS in weighing CellPro's petition. The uncertainty in the minds of CellPro's investors today is the result of a calculated business decision CellPro made in 1992 to decline a license, to infringe Hopkins' patents knowingly and willfully, to initiate costly litigation, and to gamble that Hopkins and its licensees would eventually capitulate on CellPro's terms. The filing of this petition is one more step in CellPro's aggressive litigation strategy, and this agency should not allow itself to be used by CellPro to accomplish the ambitious financial objectives of its management and investors.

Conclusion

A decision by DHHS to initiate a march-in proceeding in the circumstances of this case would be wholly unwarranted, and would send shock waves through university technology licensing offices across the country. CellPro had repeated opportunities to take a license under Hopkins's patents and refused to do so, favoring purely self-interested financial goals over the interests of patients. The Bayh-Dole Act was enacted to encourage patent licensing of potentially valuable technology invented in nonprofit institutions. Initiating a march-in proceeding to provide a compulsory license to a company that flaunted Hopkins's patent rights would have the opposite effect, greatly devaluing the incentives that are meant to be provided by the patent system. In the long run, technology transfer from nonprofit institutions to private enterprise would be chilled, and the public would be denied the benefits of their research.

Hopkins acted responsibly in patenting Dr. Civin's inventions and agreeing to license out the technology to Becton and Baxter, whose investments in research and development have succeeded in bringing the inventions to practical application. Hopkins also acted responsibly in proposing a stay of any injunction against CellPro's infringing sales pending FDA approval of a licensed alternative device in order to ensure that enforcement of its lawful patent rights will not result in any gap in the treatment of cancer patients in need of stem cell transplants. It remains committed to that pledge. There is no need, and no statutory basis, for a march-in proceeding, and Hopkins respectfully urges DHHS to deny CellPro's petition.

Respectfully submitted,

THE JOHNS HOPKINS UNIVERSITY

By its attorneys,

Donald R. Ware
FOLEY, HOAG & ELIOT LLP
1 Post Office Square
Boston, Massachusetts 02109
(617) 832-1000

Frederick G. Savage
JOHNS HOPKINS UNIVERSITY
Office of VP and General Counsel
113 Garland Hall
3400 N. Charles Street
Baltimore, MD 21218-2688
(410) 516-8128

cc. Ms. Barbara McGarey