RESPONSE OF CELLPRO, INC.

July 2, 1997

RESPONSE OF CELLPRO, INC. TO SUBMISSIONS OF JOHN HOPKINS UNIVERSITY AND IN FURTHER SUPPORT OF ITS PETITION FOR ISSUANCE OF A LICENSE UNDER THE BAYH-DOLE ACT

In its petition of March 3, 1997, and its subsequent submissions of April 24, 1997, and May 8, 1997, CellPro, Inc. ("CellPro") has set forth the basis upon which the Department of Health and Human Services ("Department") should take action under the Bayh-Dole Act to insure that CellPro's stem cell selection technology should continue to be available to citizens of this country whose taxpayer dollars funded its invention. Johns Hopkins University ("Hopkins"), the assignee of the patents which CellPro's technology has been claimed to infringe, filed an initial opposition to CellPro's petition on May 7, 1997, and CellPro responded to that opposition on May 19, 1997. Subsequently, Hopkins has filed two additional submissions with the Department, one on June 2, 1997, and another on June 17, 1997. This submission responds to the further arguments made by Hopkins in those filings.

In Part I below, CellPro addresses the claim made by Hopkins and its licensees that there is no public health need that would support a license to CellPro and shows to the contrary that failure to grant a license would have a significant adverse public health impact. In Part II below, CellPro addresses the arguments that its petition is contrary to the underlying policy of the Bayh-Dole Act and demonstrates that those policies in fact fully support the requested license. Finally, in Part III below, CellPro addresses the claim of Hopkins and its licensees that the Department lacks jurisdiction over CellPro's petition and demonstrates that in fact jurisdiction clearly exists.

I. A BAYH-DOLE LICENSE IS NEEDED TO MEET THE COUNTRY'S PUBLIC HEALTH NEEDS

In its submissions to the Department, in letters to the American Cancer Society, members of Congress, and others, and in statements to the public media, Hopkins and its licensees have repeatedly attempted to assure all concerned that there will be no adverse effect on public health as a result of the injunction they are seeking against CellPro. In fact, if Hopkins and its licensees are successful in obtaining their injunction and in forcing CellPro to withdraw its CEPRATE System from the marketplace, there will be a significant adverse impact upon public health in the United States.

A. A License is Needed to Ensure the Availability of FDA-Approved Technology to Victims of Breast Cancer, Lymphoma, and Multiple Myeloma

If the injunction requested by Hopkins and its licensees were to go into effect, patients suffering from breast cancer, lymphoma, or multiple myeloma who need stem cell transplants would have very limited access to needed technology.

Currently, the CellPro CEPRATE System is the only system for stem cell concentration and purification that is approved by the Food and Drug Administration (FDA). This system is installed in 59 transplant centers across the country. This means that a patient suffering from breast cancer or lymphoma or multiple myeloma can go to any one of those centers (or other centers as CellPro expands its product to the approximately 250 additional transplant centers in the United States) and be treated with this important technology.

If CellPro is forced to withdraw its product -- either because of an injunction's express terms or its practical effect -- patients will not have similar access to the Baxter Isolex technology. While a Baxter system is installed in 19 of the same centers as the CellPro System,[1] it has not been approved by the FDA. Accordingly, it can only be used in clinical trials in conjunction with an investigational device exemption ("IDE").[2] If there is no CellPro system available, a patient will have to hope that the local transplant center has a clinical trial in progress using the Baxter device and covering his or her disease. He or she will also have to qualify to participate in the clinical trial by meeting all of the inclusion criteria of the approved protocol and hope that the particular clinical trial is not full. Even then, there would be significant insurance reimbursement issues arising from use of an unapproved product.

Until the FDA approved the CEPRATE System in December 1996, use of the CellPro technology in the United States was similarly limited to clinical trials. After the FDA approved the CEPRATE System in December 1996, however, it became available for use as a matter of normal patient treatment by doctors. CellPro has projected that if it is not enjoined from supplying the needed technology, there will be 2,385 to 2,595 treatments using the CEPRATE System in the United States in CellPro's Fiscal Year for April 1, 1997, through March 31, 1998. Of these treatments, 1,360 to 1,520 will be normal patient treatments, not involving an IDE. In Fiscal Year 1998/1999, CellPro has projected that there will be an increase to 4,550 to 5,550 treatments, with 2,540 to 3,120 being outside the IDE context, and that in

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[1] See Exhibits Volume at Tab 1.

[2] See Declaration of David F. Weeda at Tab 2 of Exhibits Volume for a discussion of restrictions on use of devices that have not been approved by the FDA.

1999/2000 those numbers will rise to 6,710 to 9,160 and 4,120 to 5,520, respectively. If the CellPro technology is forced off the market, thousands of patients will be at risk that they will not find a place in a Baxter trial. Whatever the precise numbers, it is almost certain that a large percentage of persons who would otherwise be treated with the CEPRATE System will be unable to travel to the appropriate center and find a place in a Baxter trial for which they qualify.[3/]

Hopkins and its licensees have repeatedly tried to evade the consequences of their proposed injunction by arguing that most doctors are no longer using bone marrow transplants but rather use peripheral blood stem cell transplants. They state further that CellPro's product has not been approved for use with peripheral blood, claiming that Baxter had the foresight to concentrate on peripheral blood stem cell transplants and that it is ahead of CellPro in this area.

It is important to set the record straight. First, CellPro's premarket approval application for the CEPRATE System focused upon traditional bone marrow transplants at the direction of the FDA.[4/] This was the indication which the Agency wanted to address first. In

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[3/] CellPro has no way of knowing how many clinical trials involving breast cancer, lymphoma, and multiple myeloma are being conducted with Baxter's technology today. Nor does it have any way of knowing where such clinical trials are conducted, the details of the various protocols as they affect patient eligibility, nor the number of openings that may be available in such trials. Accordingly, CellPro has no way to estimate with any precision how many patients might be able to obtain treatment in a clinical trial and how many could not, but it is certain that the number of untreated patients would be substantial.

[4/] CellPro's PMA approval was based on the ability of the CEPRATE System to reduce toxicity in bone marrow transplants. In its submission of June 2, Hopkins tries to minimize the importance of such reductions of toxicity. CellPro continues to believe as set forth at pages 10 to 14 of its submission of April 24, 1997, that this benefit of its technology is extremely important. Further, Hopkins' statement that there are alternative methods of reducing toxicity, such as cell washing, readily available to the medical community is misleading. Cell

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consultation with FDA, however, CellPro has also conducted clinical studies of peripheral blood stem cell transplants. Indeed, CellPro has completed a pivotal randomized, controlled Phase III study of peripheral blood transplants in 130 patients as they relate to tumor cell reduction, and it will file a supplemental application for these additional indications later this summer. All of the primary end points for the study agreed to by the FDA were met. CellPro's formal Phase III trial resulted in an average 3.3 log decrease in tumor cells (99.9%), with more than 50% of the patients having no measurable tumor cells at all as shown by a highly sensitive, reliable, and sophisticated PCR assay. The median number of tumor cells infused in the selected arm of the study was 0, as compared to 2,700,000 in the unselected arm.[5/] These results compare very favorably to the claims made by Hopkins and its licensees based on preliminary results for the Baxter 300i system. Moreover, the Baxter 300i is not the product for which Baxter has sought FDA approval.[6/] In sum, Baxter's technology is in no way ahead of CellPro in this area.

[4/] (...continued)
washing techniques are unproven for reducing toxicity and can result in significant cell damage or loss, including the possible loss of the entire cell population. In effect, Hopkins proposes that patients endure either toxic reactions or other major risks and at the same time give up the "off label" benefits their physicians could otherwise have sought to provide for them.

[5/] Additional clinical trials by independent investigators have evaluated hundreds of additional patients treated with the CEPRATE System with similar results as described in numerous publications.

[6/] Baxter claims that it intends to seek to amend its PMA application to include the Isolex 300i product or to file a new application for that more advanced system. Unless the FDA applies an entirely different standard in the case of Baxter, it is difficult to see how Baxter can base an application for approval of the 300i on trials with the 300SA. (The FDA required CellPro to do a new large scale clinical trial to support expansion of its PMA for the same CEPRATE System it had approved for bone marrow use to be labeled for use with peripheral blood. The 300i is an entirely different product, and CellPro is unaware of any randomized pivotal trial that has been conducted using it.)

The Hopkins submissions claim that traditional bone marrow procedures are no longer used in this country. In fact, bone marrow transplants continue to be used and in some cases are the only procedure available. At the same time, it is correct that many physicians using the CellPro CEPRATE System have chosen to use it "off label" in performing peripheral blood cell transplants. Contrary to allegations made by Baxter, however, CellPro has not promoted its technology for use in peripheral blood procedures and will not do so until it obtains approval from the FDA.[7/] CellPro's labeling for the CEPRATE System precisely sets out the approved indication use in bone marrow transplants. Because of the numerous publications and presentations by independent investigators, doctors and patients in need of stem cell transplants know that the CellPro system can be used for peripheral blood procedures, and there is no way that CellPro can prohibit them from looking beyond the labeling and using the product for peripheral blood transplants or to reduce tumor cells in either bone marrow or peripheral blood procedures. Only if Congress were to enact legislation prohibiting doctors from using any products for an indication other than those on the label -- legislation that Congress has declined to enact -- would there be any basis for the argument that only patients receiving stem cell transplants from traditional bone marrow procedures should be considered by the Department as it weighs patient access issues presented by CellPro's petition.

[7/] The statement in Hopkins June 2 submission that CellPro has engaged in "incessant promotion" of its products for off label use is typical of the bombast that has characterized the Hopkins submissions, but it is simply not true. The only incident cited is a CellPro Christmas card that told the story of a patient being treated for childhood leukemia in a clinical trial. (A copy of this card is at Tab 3 in the accompanying Exhibits Volume.) While this warm human interest story -- appropriate at Christmas time -- may not have precisely conformed to FDA regulations regarding products under investigation, it clearly does not amount to "incessant promotion."

The argument of Hopkins and its licensees ignores the fact that patients who are treated "off label" are citizens for whom the government should and must be concerned. Their doctors are using an FDA approved device that grew out of taxpayer funded research at the Fred Hutchinson Cancer Research Center to help them avoid suffering and in some instances to save their lives, just as doctors routinely use the majority of oncology products such as chemotherapy agents that are approved for limited or even unrelated indications.[8/] Patients are no less "treated" by CellPro technology because their physicians chose not to be restricted by labeling and instead to use the CEPRATE System for peripheral blood transplants, rather than bone marrow transplants. To ignore the interests of these patients would be highly unethical. While the Baxter-CellPro dispute has been a bitter one covering a number of years, generating much heated rhetoric, it is very surprising that an institution such as Hopkins -- which plainly knows the real world of patient treatment[9/] and which itself is currently using the CEPRATE System for off label uses -- would permit such an argument to be raised in its name.

[8/] The "off-label use issue" comes up frequently in cancer treatment. Indeed, the great majority of uses for pharmaceuticals in cancer treatment are "off-label." See Hearing of the Committee on Labor and Human Resources, United States Senate, February 22, 1996, for an in-depth discussion of off-label use issues. Physicians dealing with deadly diseases experiment with new uses for products more quickly than manufacturers can apply for and obtain supplemental approvals. This is particularly true of new breakthrough technology such as the CellPro CEPRATE System

[9/] Shortly after the CellPro system was approved by the FDA, Dr. Steven Noga, Director of the Staff of Graft Engineering Laboratory at the Johns Hopkins Oncology Center predicted that a majority of treatments utilizing the CEPRATE system would be off-label over the next several years. Noga, Ishage Telegraft, Feb. 1997. (Tab 4 in the Exhibits Volume.)

B. The Possibility of FDA Approval of Baxter's Isolex 300SA Technology Does Not Satisfy the Existing Health Needs.

Currently, the Baxter Isolex system has not been approved by the FDA. According to Baxter, however, it expects the FDA's advisory panel to consider its Isolex 300SA system in late July, and approval could follow sometime late in 1997. Although Baxter has not yet filed a PMA application for its Isolex 300i, which was designed to overcome some of the problems of the earlier 300SA, the Hopkins submissions gloss over the differences between the products. Closer examination makes clear that, even if approved, the Isolex 300SA would not be an adequate substitute for the CellPro System.

CellPro, of course, does not know what is in the Baxter FDA file. Thus, it cannot predict whether the advisory panel will recommend approval of the Isolex 300SA or, if so, what the approval will encompass. While Baxter expresses optimism that the FDA will grant approval by the end of the year, the Hopkins submissions raise far more questions than they provide answers. Originally, the Isolex 300SA utilized a powerful enzyme known as chymopapain to remove magnetic beads from the separated stem cells. In its submission of June 2, 1997, Hopkins disclosed that Baxter had modified the Isolex 300SA sometime in 1995, eliminating the enzymatic release system and replacing it with a peptide release system. The Hopkins submission then goes on to note that Baxter's "application [for premarket approval] covers the Isolex 300SA, which was used in the initial clinical studies." June 2 submission at 12. What remains unclear is whether the Isolex 300SA used in the those studies utilized the enzymatic or peptide release system. If the former, it would seem that Baxter could only receive approval for a system it no longer manufactures. While such an approval would, under normal circumstances,

have no value to any company, here it would trigger the full impact of the proposed injunction and force CellPro completely out of business on the supposed rationale that an equivalent and approved product was available from Baxter. Given the constant blurring of distinctions between the Isolex 300SA and the Isolex 300i by references to the "Isolex system" in nearly every Baxter filing, and the new disclosure by Hopkins that there were actually two versions of the Isolex 300SA, Baxter's arguments may well be highly misleading.

But even if the FDA should approve an Isolex 300SA system with a peptide release system, there are real questions as to the degree to which such a product would benefit patients with breast cancer, lymphoma, and multiple myeloma. In declarations before the district court, representatives of Baxter indicated that they had replaced all of the 300SA's at Baxter-sponsored IDE sites in the United States with the Isolex 300i.[10/] In its June 2 submission, Hopkins now indicates that Baxter intends to offer both the 300SA and the 300i (if and when they are approved) for sale in the United States while noting that the 300i is more desirable than the 300SA for those "interested in consistent, routine, positive selection procedures." Hopkins June 2 submission at 12. Of course, this is the most important clinical use of the product.

Indeed, from all available evidence it appears that the Isolex 300SA is an inferior product compared to the CellPro CEPRATE System. Processing with the 300SA is slow and expensive, requiring a complete day in the processing lab. By contrast, processing with the CEPRATE System requires 1.5 to two hours. In their declarations, Drs. Ball, Burns, Burt,

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[10/] Declaration of Baxter's Dr. Bonnie J. Mills submitted in support of Baxter's motion for injunction. Dr. Mills states that "all of the Baxter-sponsored IDE sites in the United States have now substituted the 300i for the earlier model (sometimes referred to as the '300SA') retaining the 300SA version as a backup."

Champlain, DiPersio, Hesdorfer, Holland, and Parkman all note that the Isolex 300SA does not stand up to the CellPro system.[11] Dr. Calderwood specifically notes that "yields and purity with the Baxter device were not as good as those achieved with the CEPRATE S.C. device."[12]

There is thus no reason whatever to believe that, if and when the Baxter Isolex 300SA system should be approved by the FDA as Baxter predicts, physicians and institutions would utilize the 300SA system with its shortcomings as fully as they would utilize the CellPro CEPRATE System. The only real question is what portion of the thousands of patients that would otherwise receive the benefits of the stem cell separation technology will not have access to it. Whether that is a majority or only a small portion, the matter is of too great an importance for persons who are already victims of life threatening disease to become the victims of Baxter's refusal to license on reasonable terms a patent that it had no role whatever in developing, but that rather was the result of taxpayer-funded research.

C. A License Is Needed To Avoid Disruption of Ongoing Leukemia Clinical Trials, Multiple Sclerosis Treatments, and Other Critically Important Research and Development.

As explained in greater detail in CellPro's submission of April 24, 1997, the CellPro CEPRATE system is being used in over 60 clinical trials today. These include trials involving treatment of leukemia, multiple sclerosis and other autoimmune diseases, HIV therapy, solid organ transplantation, and gene therapy. CellPro projects that approximately 700 patients

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[11] See Declarations in the Appendix to CellPro's April 24 submission.

[12] Declaration of Dr. Stanley Calderwood in the Appendix to CellPro's April 24 submission.

will be treated in such clinical trials in the United States between April 1, 1997, and March 31, 1998, with another 4,000 to 5,000 patients treated in ongoing or new clinical trials over the next three years.[13/]

If the CellPro technology is forced from the market, these clinical trials and the lives of the patients involved in them will be in serious jeopardy. While Baxter has stated that it will replace any CellPro system with its own Isolex 300i system, it is clear that this could not be accomplished without far more disruption than Baxter suggests.

There are strict requirements governing investigational device exemptions under Section 520(g) of the Food, Drug and Cosmetic Act. It is difficult to obtain an IDE, and there are significant responsibilities and burdens in operating under an IDE. An investigator cannot simply substitute one device for another during the course of an investigational device exemption. The investigator must seek approval of the FDA for such substitution by cross-referencing another manufacturer's FDA master file. The FDA then determines whether the change can be made. If there is a significant difference in operating principles, it is not unusual for the FDA to place the trial on clinical hold until resolution.[14/]

Such substitution in the case of the stem cell concentration and purification technology at issue in this instance would, in all probability, require scores of investigators to start their research all over again. They would have to submit new applications for IDEs with new investigational plans, have their protocols reapproved, obtain new approvals from Institutional Review Boards which commonly meet only a few times per year, seek informed

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13/ See Tab 5 of the accompanying Exhibits Volume.

14/ See Weeda Declaration at Tab 2 in the accompanying Exhibits Volume.

consents from patients, and so on. Many months and probably one to two years would be consumed before these trials would be up and running, even if Baxter were to do all it could to assist. In the process, some promising studies would almost certainly fall by the wayside.[15/]

The declarations contained in the Appendix to CellPro's April 24 submission set out in detail the statements of physicians conducting clinical trials with the CellPro device about the impact of losing the availability of the CellPro technology. Dr. Ball notes that Baxter's device would not work for his Gaucher disease gene therapy study and that the study would have to be abandoned if the CellPro device were unavailable.[16/] Dr. Bishop notes that his clinical work would be set back by up to two years without the CellPro device and that clinical studies already in progress would have to start over as data would have to be discarded.[17/] Dr. Burt states similarly that his exciting clinical trials involving autoimmune diseases and leukemia would be shut down for at least a year, due to the regulatory and administrative delays which a change-over would entail. He notes: "the interests of my patients would be compromised --

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[15/] There are exciting developments in the use of CellPro technology occurring every day. See, e.g., the letter of Dr. James R. Berenson at Tab 6 of the Exhibits Volume. He describes a breakthrough in multiple myeloma research involving the Kaposi's sarcoma herpes associated virus (KSHV). The CEPRATE System removes the KSHV infected cells allowing patients to receive a virus-free stem cell product which may be of significant benefit to patients. It is, of course, questionable how many such studies will continue if there are no CellPro products available.

[16/] See Declaration of Dr. Edward Ball in the Appendix to CellPro's submission of April 24, Tab C.

[17/] See Declaration of Dr. Michael Bishop in the Appendix to CellPro's submission of April 24, Tab E.

fatally in some instances."[18/] This story is repeated again and again by the physicians conducting the clinical studies.[19/]

In sum, there can be no question that if the CellPro product is unavailable, there will be a major disruption in clinical trials throughout the nation. Research will be disrupted and the treatment of hundreds and perhaps thousands of patients suffering from deadly illnesses will be significantly delayed, if not discontinued. This will happen in spite of all of Baxter's promises, as Baxter well knows.

Further, there is no available Baxter technology that could be utilized in several key studies. As noted above, Dr. Ball believes the Baxter device could not be substituted for the CellPro CEPRATE System in his study regarding Gaucher disease. Dr. Parkman similarly states that his in utero program "would essentially be ended since I know of no other manufacturer that offers a system to stem cell select and T-cell deplete."[20/] Even more important, the allogeneic transplantation utilized in multicenter trials for childhood leukemia employ both the CEPRATE and the second generation CEPRATE TCD-T-Cell Depletion system. To CellPro's knowledge, Baxter has no comparable second generation product available. Even Dr. Scott Rowley of the Fred Hutchinson Cancer Research Center, a member of Baxter's scientific advisory board who is

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[18/] See Declaration of Dr. Richard Burt in the Appendix to CellPro's April 24 submission.

[19/] See Declarations of Calderwood, DePercio, Elias, Gorelick, Hesdorfer, Hesloff, Holland, Horowitz, LeMaistre, Sender, and Zaia in the Appendix to CellPro's April 24 submission.

[20/] See Declaration of Dr. Robertson Parkman in the Appendix to CellPro's April 24 submission.

often quoted by Baxter, has admitted that CellPro is ahead of Baxter in terms of developing a way to remove the donor lymphocytes thought to produce graft versus host disease.[21/]

Moreover, Baxter has only proposed to provide its technology in place of CellPro's in clinical trials that are now ongoing. Many other trials are in the planning stage, however, and there is no possible way that Baxter could fill the void that would be created by the injunction it is seeking. Not only would CellPro be precluded from pursuing such trials (for example, Phase II or III trials following successful initial testing), but it is likely that no one else would pursue them either. Certainly Baxter would not, as the recent announcement of its joint venture with VIMRX Pharmaceuticals, Inc. makes clear. According to that announcement, the research functions of Baxter's immunotherapy division, which has been responsible for the Isolex 300 technology, will soon be transferred to a new company controlled by VIMRX. According to its 10K dated March 31, 1997, VIMRX is a developmental stage company engaged in acquiring technology to develop in collaboration with other companies. It has no manufacturing capabilities and depends on third parties for significant aspects of its research and development. At the present time, VIMRX has only nine full-time employees in the United States (consisting of five executive officers, one financial analyst, and three administrative assistants), compared with the more than 60 employed by CellPro in research and development alone. CellPro spent over $75 million in developing its CEPRATE system and taking it through FDA approval and is planning to spend more than $50 million more on additional research and development over the next three years. Even if the VIMRX transaction proceeds smoothly and

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21/ See Hutchinson Publication, Tab 7 in the accompanying Exhibits Volume. See also declarations in the Appendix to CellPro's April 24 submission by Drs. Burns, Burt, Hesdorfer, and Holland.

the transfer of the technology occurs as planned, there is no basis whatever to believe that VIMRX will make up what would be lost on account of a CellPro injunction, and the adverse consequences to the public health two or three years in the future could be even greater than those that would inevitably occur in the immediate term.

D. The Claim that CellPro Should and Would Simply Continue to Support Needed Research and Development and Clinical Trials is Wholly Unrealistic.

Hopkins and its licensees have attempted to argue that the injunction they are seeking in court will have no adverse effect on CellPro's research and development activities, clinical trials, or patient treatment. In doing so, they rely largely on the supplemental declaration of their expert, Dr. Hausman. In Dr. Hausman's view, CellPro can be expected (1) to spend its available cash (apparently including cash CellPro anticipates being ordered by the district court to set aside to pay a potential judgment for damages and attorneys fees) to support its stem cell system at the same level it would spend if it had a Bayh-Dole license, and (2) simply to go to the capital markets for additional funds when its cash runs out. Moreover, CellPro should do so in the face of an injunction that would first turn each sale into a loss, and then completely prohibit any use of CellPro's technology, potentially within months.

At the outset, if the prediction in the Hopkins submission that Baxter will obtain FDA approval for its Isolex 300SA product in 1997 is accurate, Dr. Hausman's arguments are largely irrelevant. For under the proposed injunction, FDA approval would trigger an absolute ban on new clinical trials, as well as new phases of existing trials. Such a ban would essentially bring an end to CellPro's operations, in the process ending the cash drain caused by new market

introductions and ongoing research and development (and probably making it unnecessary to seek additional funding). But as discussed above, in the process such a ban would also strand a large number of patients both in and outside of clinical trials without a meaningful source for stem cell therapy.

In fact, Dr. Hausman's supplemental declaration was directed at the analysis by CellPro's chief financial officer Larry Culver of the impact of the proposed injunction based on an assumption that there would be no approval of a Baxter product until 1999. Mr. Culver's declaration explains why, even though Hopkins and its licensees purport not to ask for a ban on product sales or support of clinical trials pending such approval, the practical effect of the injunction they are seeking would be almost the same. The attempt of the Hopkins submission to claim otherwise is simply nonsense.

Dr. Hausman's second declaration is as riddled with errors as his first.[22/] To expect CellPro to support research and development and clinical trials at the same level that would occur if CellPro had a Bayh-Dole (or other) license is completely unrealistic. Indeed, Hopkins and Baxter have designed their proposed injunction so as to prevent such support. The proposed injunction would require payment to Baxter of a royalty equal to the greater of $2,000 or CellPro's total "incremental" profit. Such a royalty means that CellPro would be unable to recover any of its research and development or overhead costs and in all likelihood would not

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22/ In his initial declaration, Dr. Hausman asserted that CellPro could simply use revenues from the sale of other products to cover its stem cell research and development and other "fixed" costs. Faced with the obvious fact that CellPro, as a single product company, must recover its research and development and overhead costs, if at all, from sale of its stem cell products, Dr. Hausman retreats to the assertion that CellPro could simply go to the capital markets to finance these costs while pursuing an appeal of the injunction and continuing to support its stem cell technology at an undiminished rate.

even recover its cost of manufacture. Dr. Hausman does not address directly the impact of such an injunction on expenditures to support research and development or clinical trials, but simply assumes that CellPro would be able to support such a level of expenditures consistent with its obligation to its shareholders. In fact, as Mr. Culver's declaration shows, without a license to ensure that it could continue to market its stem cell products, CellPro would have no choice but to substantially reduce expenditures on clinical trials, on research and development, and on other overhead in order to minimize the adverse consequence of the injunction, during the period between its entry and the resolution of an appeal.

Submitted herewith is a letter from James Scopa, Managing Director of Alex. Brown, an investment banking house which makes a market in CellPro stock and which has written equity research on CellPro.[23/] Mr. Scopa's analysis makes clear that Dr. Hausman's conclusions concerning CellPro's ability to raise funds in the capital market are without any basis. Contrary to Dr. Hausman's assertions, Mr. Scopa concludes that:

> In our opinion should the injunction be granted as currently drafted, and no agreement on a commercially reasonable royalty be reached, CellPro will not be financeable in the public or private equity markets .... In this case, Alex. Brown or any other underwriter or placement agent would be asking investors to finance the company on the unassessable probability that within two years a federal appeals court will overturn the findings of the trial court on multiple issues. We do not believe investors will be willing to finance the Company on that basis without some reasonable royalty arrangement achieved between the litigants (emphasis added).[24/]

[23/] CellPro's Board of Directors has recently retained Alex. Brown to provide financial advisory services to assist CellPro in dealing with the consequences of the Baxter litigation.

[24/] Tab 8 in the accompanying Exhibits Volume. In his letter, Mr. Scopa sets forth his analysis in some detail and concludes as follows:

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The lack of relationship between Dr. Hausman's analysis and the real world is further reflected in the assessment of his analysis done by Marc Ostro, a securities analyst who follows CellPro. He has characterized Dr. Hausman's assertion that CellPro could obtain funds as "comical" and not one that would be accepted by any "sane person."[25/]

Dr. Hausman's arguments in fact border on the specious. He asserts that CellPro was able to obtain initial funding despite the market's knowledge of the Hopkins patents, and

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[24/] (...continued)
Finally, although in the past Alex. Brown has financed biopharmaceutical companies involved in on-going patent litigation, CellPro's current situation is quite different from past financing candidates in several important respects. First the intellectual property at issue underlies a fundamental commercial component of its only approved product as well as substantially all follow-on products currently under development for commercialization near-term. Second, the stage of the legal proceedings with an adverse outcome to CellPro is far more advanced than any company we can identify who has attempted to finance in the capital markets.

[25/] Mr. Ostro's analysis, attached at Tab 9 of the accompanying Exhibits Volume, states:

> The professor went on to say that it will make sense for [CellPro] to keep selling the product, even at a loss, to keep customers happy so when their next product is launched there will be a receptive marketplace.
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> We must admit to being rendered speechless by this remarkable piece of business acumen. CellPro does not make any other near term product devoid of the anti-CD34 antibody component, thus the professor is suggesting that CellPro keep selling CEPRATE until they run out of money, and while doing so, build a marketplace for Baxter when and if they get Isolex approved. If this were not such a serious matter it would be comical. Given that the costs of goods for CEPRATE is currently about 50% and costs of sales of such products is close to 30%, adding a 50% royalty means that for every $4,000 column CellPro sells they will lose $1,200. We do not think that this logic will persuade the Secretary of the Department of Health and Human Services or any other sane person that, under the terms of Baxter's 'newest' request, CellPro will be able to keep CEPRATE on the market. Hence, we believe that Bayh-Dole still applies and should be viewed as a real threat to Baxter's latest position.

consequently it could seek additional funding despite the injunction. But there is a vast difference, as noted in Mr. Scopa's letter, between knowledge of the existence of such patents, accompanied by an opinion of counsel that those patents were invalid, and the situation today, where the initial jury verdict in CellPro's favor has been set aside in favor of a judicial finding of both validity and infringement and where final determination on an injunction request is pending.

Similarly, Hausman argues that CellPro will eventually have European sales, and that should be enough to motivate CellPro to support its current levels of research and development. Certainly, the prospect of European sales creates incentives to continue some level of research and development. But it gives little or no incentive to support U.S. clinical trials on products already licensed in Europe. And whatever incentive there is, it is further reduced by the provision in the proposed injunction that would effectively eliminate CellPro's European sales -- notwithstanding that the Hopkins patents are not and never were issued outside the United States.

In the end, Hausman simply asserts that the hypothetical availability of funds from the capital market means that the management of CellPro will not do what economic forces as well as management's duty to shareholders would demand -- namely, to take all action necessary to minimize the adverse consequences of the proposed injunction, which in this case would cause CellPro to reduce expenditures to the minimum level necessary to preserve its position and to exploit the possibility that it will ultimately prevail on appeal.[26/]

[26/] Contrary to the claims made in Hopkins June 2 submission, there is no conflict between what Mr. Culver said in his declaration and what CellPro has told its investors.

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In sum, no matter how loud Baxter, Hopkins, and Becton Dickinson shout that no patients will lose access to needed technology if they obtain their sought after injunction, the facts do not bear this out. Patients need treatment now. Baxter's products will not be able to fill the void and reach people who need assistance in and out of clinical trials. Since Hopkins and its licensees have refused to negotiate a license on reasonable terms and conditions that would permit CellPro to continue to make its technology available to those who need it, the public health can only be satisfied by the issuance of such a license under the terms of the Bayh-Dole Act.

II. THE POLICIES OF THE BAYH-DOLE ACT STRONGLY FAVOR THE EXERCISE OF MARCH-IN RIGHTS IN THE PRESENT CASE

Hopkins' June 2 submission argues at page 4 that granting CellPro's petition "would undermine the purposes of the Bayh-Dole Act." On examination, however, what Hopkins really claims is that any exercise of march in rights would have that effect and that Congress somehow erred when it provided for march in based on a finding of either delay or health needs. Both of these arguments are precluded by the express language of the statute and

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26/ (...continued)
CellPro's 10-K filed on June 27, 1997, discusses Mr. Culver's declaration and makes clear that if the injunction were to issue in the form sought by Hopkins and its licensees and CellPro is unable to obtain a Bayh-Dole or other license, CellPro "would likely find it necessary to significantly restrict operations so as to conserve capital while awaiting the outcome of the appeal." Tab 10 of the accompanying Exhibits Volume. Of course, CellPro hopes to avoid such *reductions and is pursuing every opportunity (including these proceedings) to do so; but it is* simply unrealistic to think that CellPro would be able to avoid drastic reductions in research and development, clinical trials, and patient treatment, with all of the adverse impact on the public health such reductions would entail.

applicable regulations and should be rejected. Baxter, Becton Dickinson, CellPro, and numerous other companies have taken licenses subject to the government's march in rights. There is no reason whatever to think that the parade of horribles recited in the Hopkins submission would come to pass or that the policies of the Bayh-Dole Act would be adversely affected in any way if the CellPro petition were granted. To the contrary, as discussed below, those policies provide strong reasons for the grant of the petition.

A. Hopkins' Claim that Granting CellPro's Petition Would Create Incentives that Would Destroy the Bayh-Dole System Is Without Merit.

At the same time Hopkins and its licensees accuse CellPro of using "scare tactics" by pointing out the effects the injunction being sought would have on CellPro and those who would otherwise benefit from the CEPRATE System, the Hopkins submissions engage in such tactics of their own, claiming that granting CellPro's petition would "effectively destroy the system the Bayh-Dole Act was meant to create" and "have a disastrous effect on future licensing of university-based technology." June 2 submission at 7-8. That former Senator Bayh, who has had a long-time interest in furthering such technology signed the petition on CellPro's behalf, should be answer enough to the claim, which in any event is wholly without merit.

The Hopkins June 2 submission claims without any support that granting CellPro's petition would provide an incentive for "any medical products or pharmaceutical company" to pursue "bad faith litigation, and then, if it loses in court," to demand a compulsory license "on financial terms it could never have achieved through voluntary negotiation." Id. at 1, 6. According to Hopkins, if the Department were even to initiate a march in proceeding, "no

company will again invest with confidence in the potential inventions of a university or hospital that received even a modicum of federal support." Id. at 3.

Even a cursory examination makes clear that the scenario Hopkins attempts to paint has no basis in fact. With regard to the supposed risk that a march in applicant would receive "an unfair competitive advantage" by obtaining a license on unreasonable terms, id. at 1, the Bayh-Dole Act itself provides the answer. Under the Act, the Department can only issue a Bayh-Dole license "on terms that are reasonable under the circumstances." 35 U.S.C. § 203. CellPro's petition has never sought anything else. See CellPro's April 24 Submission at 38 ("CellPro requests that the Department of Health and Human Services immediately exercise its march-in rights to require Johns Hopkins to issue CellPro a license to the Civin patents on reasonable terms or to issue such a license itself").

It is true that CellPro has long maintained that 4% would be a reasonable royalty for a non-exclusive license to use the patents at issue.[27/] Nevertheless, as the Department knows, to ensure continued patient access to its technology, CellPro has proposed to take a license on terms more favorable to Baxter than those Baxter says were available to CellPro and that Baxter agreed to in licenses with other companies.[28/] It would thus be CellPro that would be at a competitive disadvantage, not Baxter. But Baxter rejected CellPro's offer out of hand unless it

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[27/] How Baxter can justify saying, as it has maintained in litigation, that it could reasonably demand $1 million and a 10% royalty (an 80% markup) from CellPro for a non-exclusive license when Baxter had added no value to the technology since entering into an exclusive license from Becton-Dickinson -- which as discussed below Becton-Dickinson had no right to give -- for $1.25 million plus a 5.5% royalty only three months before has never been explained.

[28/] See Tab 11 in the accompanying Exhibits Volume.

could also ensure that the Hopkins patents would not be subject to challenge in court.[29/] Under the patent laws, however, Baxter cannot demand royalties on an invalid patent or a patent that would not be infringed by the CellPro technology or require that a licensee not challenge its patent monopoly. See Donald S. Chisum, Chisum on Patents § 19.02[3] (1997). Once again, it is Baxter's attempts to demand what it has no right to obtain -- first, rights to CellPro's product in Europe and, now, immunity from challenge to the Hopkins patents -- that has prevented this matter from being resolved through voluntary negotiation and turned instead into a matter of patent law roulette with the public health as the stakes.

Hopkins' claim that granting CellPro's petition would encourage others to follow CellPro's example and lead to future litigation and demands for the exercise of march in rights is as unfounded as its claim that CellPro has refused a reasonable license. In fact, the example presented by CellPro proves the opposite point. On the basis of an opinion by its patent counsel and at great expense, CellPro challenged Baxter's overreaching demands and later obtained a jury verdict that its technology did not infringe and that the Hopkins patents were invalid, only to see that verdict later set aside by a judge. That CellPro now faces millions of dollars in claims for treble damages for "willful infringement" and attorneys' fees makes clear that the patent laws provide strong disincentives, not incentives, to litigation, and that the scenario painted by Hopkins is unlikely ever to exist.

But even if in the future someone should challenge one of the some 10,000 patents claimed to have been licensed over the past five years under the Bayh-Dole provisions, it would still have to meet the public health or delay criteria of the Act. And the prospect that a

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29/ See Tab 12 in the accompanying Exhibits Volume.

march in license might be issued once every 15 or 20 years to ensure that the public in fact receives the benefits of taxpayer funded research could hardly be thought to undermine the purposes of the Act. Indeed, where action is required to achieve patient access to technology (arising from publicly funded research) that will alleviate suffering and save lives, both the Act and good public policy clearly call for the exercise of march in rights. The marketplace for technology can certainly weather the few instances where this occurs.

B. Grant of the Petition Would Further, not Impair, the Policies of the Act

As the Hopkins submissions note, the primary purpose of the Bayh-Dole Act was to remove what were considered obstacles to the commercial use of inventions that resulted from government-funded research under the pre-Bayh Dole law, whereby rights to inventions made by grantees belonged in the first instance to the government. Under the Act, ownership was vested in the grantee institution subject to various rules and regulations, including the retention by the Government of march in rights where there is nonuse or unreasonable use of a patent. Grantee institutions, in turn, were expected to license patents that they received, again subject to various rules and regulations, and to use the resulting royalty income to fund additional research.

In the case of most discoveries and resulting patents, there is no reason to believe that the usual rules will not serve the public interest, and the passage of more than 15 years without a serious dispute over march in rights reflects the correctness of the congressional judgment. Where, however, the government funds basic research and the grantee institution seeks and obtains broad patent rights that threatens to preempt discoveries critical to the public

health made by subsequent grantees pursuing other federally funded research, the public interest is jeopardized and the march-in policy rightly comes into play.

1. March-In is Particularly Appropriate Where the Use of the Patent Resulted from the Subsequent Research that is Now Threatened to Be Blocked.

As set forth in prior CellPro submissions, shortly after Hopkins filed the patent application in 1984 that eventually resulted in the patents on stem cell suspensions, it entered into an exclusive license to Becton Dickinson. Becton Dickinson was able to use the My-10 antibody to develop diagnostic products, which it did by 1985. However, there were problems that prevented Becton Dickinson from turning its diagnostic work into therapeutic products -- most significantly that My-10 did not work on animals so there was no real way to test the theory that a suspension of stem cells could substitute for bone marrow in regenerating the blood and immune system after high dose chemoradiation therapy.

It was at this point that the government funded research at the Fred Hutchinson Center paved the way for the use of stem cell technology in human patients. That research resulted first in the discovery of the 12.8 antibody, which has different characteristics than My-10 and could be used in animal studies. It also resulted in the development of a system for isolating the antibody and the cells it recognized in large quantities so that human studies could proceed promptly thereafter. As a result, CellPro was formed in 1989 to commercialize the Hutchinson Center's inventions. It immediately began planning Phase I and II clinical trials, and it sponsored its first stem cell transplants in human patients in 1991 and sought PMA approval of its CEPRATE System from the FDA in 1993. By contrast, according to Appendix E of the Hopkins June 2 submission, Baxter did not even sponsor its first trial until 1993 and did not file

a PMA application (for the Isolex 300SA) until 1997, more than 12 years after Hopkins first licensed its patents.

Had Hopkins sought to prevent the Fred Hutchinson Center from pursuing stem cell technology in 1987 or 1988 on the basis of its government financed patents, it seems plain that the Department would not have hesitated to order the issuance of a march in license. For otherwise the Hopkins patents would have remained untested and unused for any therapeutic use, and stem cell technology would have been set back for years. But the same lack of use and delay that would have supported such a license then also supports a license now. After all, the policies of the Bayh-Dole Act were designed to bring to commercial use the fruits of government research at the Hutchinson Center just as much as that done at Hopkins. Baxter's refusal to grant a license on reasonable terms prevents the subsequent grantee from benefitting from the commercialization of its work and is in conflict with the policies underlying the Bayh-Dole Act. Granting CellPro's petition and ensuring a reasonable license and the benefits envisioned from taxpayer funding of research would overcome these artificial obstacles to the realization of such benefits and serve the policies that led to the Act's enactment.

2. The Bayh-Dole Policy in Favor of Small Business Further Supports the Granting of CellPro's Petition

In its June 2 submission, Hopkins claims that Congress intended by the Bayh-Dole Act "to encourage exclusive licensing as the most effective means to assure commercialization of new medical technologies." June 2 Submission at 5. (Emphasis in original.) There can be no question that Congress authorized exclusive licensing and that it considered such authorization likely to further commercialization of the fruits of government

funded research. In doing so, however, Congress also made clear (1) that exclusive rights would be subject to march-in rights when the public interest demanded and (2) that whenever possible large pharmaceutical companies like Baxter not be the beneficiaries of long term exclusive licenses, but rather that when a small business was able to use the technology, there should be a strong preference for the exclusive license to go to such a firm.[30/] The plain violation by Hopkins and its licensees of the Act's requirement that small businesses be given preference "except where it proves infeasible after a reasonable inquiry" provides further grounds for granting the requested license.

Hopkins and its licensees do not attempt to deny that -- notwithstanding that CellPro had been formed the prior year for the specific purpose of commercializing stem cell technology and that Hopkins' expert witness testified that CellPro would have agreed to pay more for a license in 1990 than Baxter did -- that they made no effort to inquire about the existence of a suitable small business and that CellPro was not offered a license at the time Baxter obtained its exclusive license to the Hopkins patents. Rather, they have urged that the

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30/ As the House Committee on Small Business noted in reporting on that body's version of what became the Bayh-Dole Act, "High-technology, innovative small businesses have been found to provide the greatest advances in the country's technology base for a given investment of resources. Their involvement in the innovation process is greatest at the riskiest stage, that of invention where major new breakthroughs are made. Thus, promoting the involvement of the small business sector in research and development, and specifically in federally funded efforts, can provide significant benefits to the economy beyond those to be gained from investment elsewhere." H.R. Rep. No. 96-1006, 96th Cong., 2d Sess. at 37 (1980).

From the results of the five-year survey attached to the Hopkins June 2 submission at Exhibit A, it appears that the small business preference has been at least partially effective: According to the study, some 1,500 companies (including CellPro) have been started as a result of Bayh-Dole licensing, with 464 such companies having been started in 1994 and 1995 alone.

small business preference somehow did not apply because Baxter obtained its license from Becton-Dickinson, not Hopkins, and that in any event the applicable regulations provide no remedy for a violation of the law.

With regard to the first attempted justification, there is no reason whatever to believe that Congress did not intend the small business preference to apply when Baxter obtained its license to the Hopkins patents. In fact, it is questionable whether Becton-Dickinson even had the right to grant Baxter an exclusive license.[31/] In any event, the policy of the small business preference plainly applies as much to a later exclusive license as to an early one and under that policy CellPro, not Baxter, should have been offered the license which Becton-Dickinson could not use.

Hopkins' second argument is based on the provision in the regulations that it is in the discretion of the grantee, not the Department, to decide when the small business preference should be applied. Whether the regulations properly carry out the intent of the law in this respect is questionable to say the least. But Hopkins argument misses the point in any event, for there is no argument that Hopkins or anyone else exercised any discretion in the matter: They all simply ignored the law. CellPro is not at this juncture asking the Department to invalidate Baxter's license to the Hopkins patents. It is, however, asking the Department to take account of the violation of the small business preference and that fact that CellPro, not Baxter, should have received the license in the first place, when it acts on CellPro's Bayh-Dole petition. For those

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[31/] At the time Becton Dickinson received its license, the law was somewhat different and permitted an exclusive license to be granted to a large business, but limited the period of exclusivity to five years from first commercial use of the patent. Since Becton Dickinson began to use the patents in 1985, it would appear that any exclusive rights it had (and that it could therefore sublicense to Baxter) would have expired in 1990.

facts are plainly relevant (1) to whether Baxter's refusal to license CellPro and instead to try to force it out of business calls for the exercise of march-in rights under all of the circumstances, and (2) to the reasonable terms upon which a Bayh-Dole license should be issued to CellPro to permit it to continue to serve the public health needs of the country.

III. THE CLAIM BY HOPKINS AND ITS LICENSEES THAT THE DEPARTMENT LACKS JURISDICTION OVER CELLPRO'S PETITION IS WHOLLY WITHOUT MERIT

In both its May 7 and June 2 submissions, Hopkins contends that the Department does not have jurisdiction under the Bayh-Dole Act to initiate a march in proceeding with regard to the Hopkins patents. This contention is wholly without merit.

The Bayh-Dole Act, which took effect July 1, 1981, states in relevant part that "the Federal agency under whose funding agreement the subject invention was made shall have the right...to require the contractor, an assignee or exclusive licensee of a subject invention to grant a . . . license . . . to a responsible applicant . . . upon terms that are reasonable..." (emphasis added). 35 U.S.C. § 203. The statute defines a "funding agreement" as "any contract, grant or cooperative agreement entered into between any Federal agency... and any contractor for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government," 35 U.S.C. § 201(b), and defines a "subject invention" as "any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement" 35 U.S.C.§ 201(e).[32/]

[32/] The statute further defines the term "made" to mean "the conception or first actual reduction to practice of such invention." 35 U.S.C.§ 201(g).

Although there may be a question in this case as to the date that Dr. Civin performed the fusion that resulted in the My-10 hybridoma,[33] the evidence discussed below is overwhelming that he discovered the characteristics of the My-10 antibody which he later claimed in the patents that later issued to him and assigned to Hopkins under the auspices of an NIH Grant which commenced in May of 1982. It was not until after Dr. Civin discovered these characteristics that the invention he claims was reduced to practice. Accordingly, under the terms of the statute, the invention claimed in the Hopkins patents was clearly made during the term of a "funding agreement," and the Department has the right to initiate a march in proceeding with regard to those patents.[34]

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[33] Johns Hopkins contends in its May 7, 1997, filing that Dr. Civin made the hybridoma in May, 1981. We do not have access to the information which might permit us to verify this contention. In any case, the date which Dr. Civin made the hybridoma is not relevant for purposes of Bayh-Dole jurisdiction. Under the Act, the only date which is relevant is the date on which the invention was conceived or reduced to practice.

[34] In all likelihood, even conception did not occur until well into the period of the NIH grant. In Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991), the court held that "Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it." Id. at 1206. Thus, it does not matter when Dr. Civin performed the fusion that resulted in the My-10 hybridoma. Conception occurred only after he discovered the properties claimed in the patents.

Moreover, even if Dr. Civin had conceived of the invention and reduced it to practice in May of 1981 as Hopkins seems to suggest, the Department would still be able to issue the requested license under the terms of the pre-Bayh-Dole regulations. From the time he joined Hopkins, Dr. Civin's research work was supported in part by a "CORE" Regional Oncology Center Support Grant (NIH-NCI Grant # CA 06973). See Testimony of Dr. Civin, March 4, 1997, in Johns Hopkins Univ. v. CellPro, Civ. Action No. 94-105, at p. 197, L. 13-25; p. 198, L. 15-20 (D. Del.) (Tab 15 in the accompanying Exhibits Volume). Pursuant to the pre-Bayh-Dole regulations, ownership of any inventions made by Dr. Civin with this NIH support before the effective date of the Bayh-Dole Act would have been the property of the United States and subject to an assignment of rights by a determination of the Assistant Secretary for Health under

(continued...)

Dr. Civin applied for a "Department of Health, Education and Welfare Public Health Service Grant" for work entitled "Antigenic Analysis of Hematopoiesis" on June 19, 1981.[35] The grant application, for research to begin April 1, 1982, proposed "further development and use of murine and human monoclonal antibodies, specifically directed against small subsets of myeloid cells, to approach the identification and isolation of human hematopoietic precursor cells .... Resulting antibodies will be used to isolate precursor cells, and to study hematopoiesis in model systems."[36] (Emphasis added.) According to his grant application, Dr. Civin was seeking funding for research into monoclonal antibodies that would bind to stem cells. Even if it is not exactly clear when Dr. Civin performed the fusion that resulted in the My-10 hybridoma disclosed in the patents, it is clear that at the time of his grant application he had not yet done the extensive characterization work necessary to discover whether the hybridoma produced an antibody that had the useful properties he was seeking, and which he eventually disclosed and claimed in his patents.

Other grant documents confirm that it was during the term of the grant that Dr. Civin performed the tests necessary to describe and characterize the My-10 antibody and hybridoma in terms of the pattern of reactivities which, eventually, he was to specify in his patent claims. At the conclusion of the first year of his NIH Grant, Dr. Civin applied for a continuation grant. In his summary of the work proposed for year two of the grant, he indicated

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[34] (...continued)
45 C.F.R. § 8.2.

[35] Relevant portions of Dr. Civin's application (the "NIH Grant Application") are submitted herewith at Tab 13 in the accompanying Exhibits Volume.

[36] NIH Grant Application at JH052179.

that he had still not fully investigated what types of cells the My-10 antibody would bind to. He explained that under the continuation grant he planned to "test these monoclonal antibodies for binding to an array of (in vitro) colony-forming cells."[37] As part of the same application, in the section describing his first year results, he reported that the characterization of the My-10 antibody, "is progressing" but that the work had not yet been completed: "Work in progress will fully characterize the cellular distribution of the My-10 antigen, but it is already clear that My-10 is unique in its expression on cell surfaces of hematopoietic progenitors, but not on mature myeloid cells of any lineage."[38] (Emphasis added.) This further confirms that the characterization of the My-10 antibody was not completed in the first year of the NIH Grant (5/1/82 through 4/30/83), and continued into the second year.

In his application for a third-year continuation grant, Dr. Civin noted an invention "not previously reported."[39] Under the heading "Invention," he listed an invention titled "Human Stem Cells and Monoclonal Antibodies," with himself as inventor, and with patent applied for on February 6, 1984 -- the filing date for the Hopkins patents.[40] The prior year's application expressly stated that there were no unreported inventions, and there can thus be no real question that Dr. Civin himself thought that he had discovered the invention disclosed in the patents during the second year of the NIH Grant.

37/ NIH Grant Application at JH052247, JH052250.

38/ NIH Grant Application at JH052252-53.

39/ NIH Grant Application at JH052260, Box. No. 11.

40/ NIH Grant Application at JH052261.

Dr. Civin's trial testimony further corroborates that his research into the pattern of reactivities of the My-10 antibody spanned several years and concluded (if not began) during the term of the NIH Grant. In the 1995 trial, Dr. Civin testified:

> Q. Did you take any steps to tell the scientific community about your discoveries in this respect?
>
> A. Yes, I did. In 1984, our paper describing these results was published in the Journal of Immunology. This paper described these two years of work and the conclusions we came to, saying that we had --- that we had identified a stem cell-specific antibody and antigen called My-10 antibody and My-10 antigen.[41/] (Emphasis added)

At the second trial in 1997, Dr. Civin testified:

> Q. And could you tell us the time period of the -- the time period in which you were doing the work that led up the CD34 antigen discovery?
>
> A. Well, I started that work in around 1981. A couple of years after starting my lab, as I said before I started off working on the granulocytes and moved to the stem cells when I got the courage to approach this needle in the haystack problem. And in a couple of years subsequent to that, we did the studies which really characterized the expression and the importance and other details of this molecule that was affectionately called My-10 and later a group of scientists called CD34.[42/] (Emphasis added)

In addition to Dr. Civin's statements in his continuation grant application and at both trials, further support for the fact that the important characteristics of the My-10 antibody were discovered during the term of the NIH Grant is found in the articles he published during the term of the grant. For example, Dr. Civin's February 1983 Hybridoma abstract re "Cell Surface

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41/ Testimony of Dr. Civin, July 25, 1995, in Johns Hopkins Univ. v. CellPro at p. 120, L. 5-13 (Tab 14 in the accompanying Exhibits Volume).

42/ Testimony of Dr. Civin, March 4, 1997, in Johns Hopkins Univ. v. CellPro at p. 133, L. 17-25; p. 134, L. 1-4 (Tab 15 in the accompanying Exhibits Volume).

Antigens Defined by Four Monoclonal Antibodies Raised Against KG-1a Cells" acknowledges support from three NIH grants, including NIH Grant # CA 32318.[43] In addition, Dr. Civin's July 1984 Journal of Immunology paper "Antigenic Analysis of Hematopoiesis" notes in footnote 1 that the work "was supported in part by National Institutes of Health Grants" including Grant No. CA32318.[44]

If there were still any question in light of the foregoing, the '680 patent includes a certificate of correction, dated January 31, 1989, which expressly inserted the following words beneath the title of the patent:

> The invention described herein was made in the course of work under a grant or award from the Department of Health and Human Services.[45]

Moreover, the license agreements entered into between Becton-Dickinson and Baxter, and Baxter and Applied Immune Systems ("AIS") both acknowledge the Department's rights in the patents pursuant to the Bayh-Dole Act. For example, the license agreement between Baxter and AIS includes the following clause under the heading Government Rights: "All rights granted by BAXTER to LICENSEE under this Agreement are subject to the requirements of Public Law 96-517 [the Bayh-Dole Act], as amended, and any applicable implementing regulations." [46] And

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[43] Tab 16 in the accompanying Exhibits Volume.

[44] Tab 17 in the accompanying Exhibits Volume.

[45] Tab 18 in the accompanying Exhibits Volume.

[46] Non-Exclusive License Agreement between Baxter Healthcare Corporation and Applied Immune Sciences, dated December 23, 1992, Article III (Tab 19 in the accompanying Exhibits Volume).

the license agreement between Becton-Dickinson and Baxter contains virtually identical language.[47/]

In sum, under the auspices of his NIH Grant, which covered the period May 1, 1982, through April 30, 1985, Dr. Civin did the work which led to the discovery of the My-10 characteristics claimed in the Hopkins patents. Even if, as Hopkins contends, Dr. Civin first made the My-10 hybridoma in May of 1981, it is clear from his grant applications, journal publications, trial testimony, and other evidence that he did not discover the critical properties he claims in the patents and did not reduce the invention to practice until well after the commencement of the NIH Grant period. Pursuant to the terms of the Bayh-Dole Act, therefore, the Department has the right to grant the march in license requested by CellPro's petition.

[47/] March 5, 1997, proceedings in Johns Hopkins Univ. v. CellPro at p. 268, L. 3-13 (Tab 20 in the accompanying Exhibits Volume).

IV. CONCLUSION

For the reasons stated above and in CellPro's prior submissions, the Department of Health and Human Services should grant CellPro's petition.

Respectfully submitted,

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