DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
Office of the Director

Office of Extramural Research
Building 1 Room 144
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BETHESDA, MARYLAND 20892
http://www.nih.gov/grants/oer.htm

MAR 21 1997

Mr. Ronald R. Peterson
President
Johns Hopkins University
Houck Building Room 193
Baltimore, MD 21287

Dear President Peterson:

This is to inform you of the enclosed petition made to the Department of Health and Human Services (DHHS) by CellPro, Incorporated that the DHHS exercise its authority under 35 U.S.C. 203 to issue a license or require the current exclusive licensee to sublicense certain technology developed at the Johns Hopkins University (JHU) under grant funding by the National Institutes of Health (NIH).

Pursuant to the regulations implementing Section 203, 37 C.F.R. 401.6(b), we are requesting written or oral comments from JHU on the petition, as well as any other information relevant to this matter. We draw your attention to the criteria contained in paragraph (j) of the Patent Rights Clause set forth at 37 C.F.R. 401.14(a) that will be used in making the determination to grant or deny the petition. In particular, we request that you provide all pertinent information, supported by factual documentation and evidence, with regard to criteria (1) and (2), pertaining to, respectively, commercial development activities of the current licensee(s) and health or safety needs which exist with regard to this technology. If any of the documentation you submit is confidential or proprietary to you or your licensee(s), please ensure that it is clearly marked as such.

You may submit comments to me at the above address, with a copy to Ms. Barbara McGarey, Deputy Director, NIH Office of Technology Transfer, 6011 Executive Blvd., Suite 325, Rockville, MD 20852. If you have any questions, please do not hesitate to contact me directly at (301) 496-1096 or Ms. McGarey at (301) 496-7057.

Sincerely,

Wendy Baldwin, Ph.D.
Deputy Director for Extramural Research, NIH

Enclosure

cc:
Mr. Howard Califano, JHU

interest. Accordingly, on behalf of our client, CellPro, Incorporated, the company whose product has been approved by the FDA, we ask that you exercise those rights to require that a license be issued to the extent necessary to ensure that the product remains on the market or, if necessary, issue such a license yourself.

Background of the Request

The human body normally manufactures millions of blood and immune system cells each day. These cells are the product of stem cells that exist in bone marrow and that reproduce and develop into all of the cells of the blood and immune system. When stem cells are destroyed by disease or radiation therapy, the only treatment possible is often a bone marrow transplant in which stem cells are harvested from bone marrow or blood and given to the patient to reconstitute the patient' s blood and immune system.

Stem cells constitute a small portion of all cells that exist in bone marrow. The more mature blood cells in bone marrow may, when transplanted, carry disease present in the donor cells or trigger a potentially fatal immune response (called graft versus host disease) in the transplant recipient. In 1980, Drs. Koeffler and Golde, working under a federal grant at the University of California at Los Angeles, suggested a way to overcome these problems when they identified proteins that appeared uniquely on immature cancer cells. They postulated that stem

cells would contain similar proteins or antigens that would permit their "positive" selection through the use of monoclonal antibodies.[1/]

Shortly thereafter, Dr. Curt Civin at the Johns Hopkins Oncology Center in Baltimore, Maryland, was working under a grant from the National Institutes of Health for further bone marrow cell research. Following the approach proposed by Drs. Koeffler and Golde, Dr. Civin discovered a monoclonal antibody which he named My-10. The My-10 antibody binds with an antigen on the surface of stem cells but not on most mature blood cells. Scientists working in this area subsequently clustered the My-10 antibody with other antibodies under the designation CD34 (the CD being for "cluster designation"). Dr. Civin published a paper describing his research in July 1983 and filed a patent application arising out of that work in February 1984.

Soon after Dr. Civin filed his patent application but before any patent had issued, scientists at the Fred Hutchinson Cancer Research Center in Seattle, Washington (the "Hutchinson Center"), were engaged in stem cell research under a different NIH grant. In the course of that research, the Hutchinson Center scientists discovered a monoclonal antibody they called 12.8. Like My-10 and several other subsequently discovered antibodies in the CD34 cluster, the 12.8 antibody binds with an antigen on the surface of stem cells. The 12.8 antibody

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[1/] Other scientists had previously reported on the successful use of monoclonal antibodies that attached to mature blood cells but not to immature cells, thereby permitting the isolation of immature cells by "negative" selection. "Positive" selection targets the desired cells directly and may provide for a simpler and more effective process.

differs, however, in that it binds in 10 places rather than two as does My-10. Moreover, in other work, Dr. Ronald Berenson and his colleagues at the Hutchinson Center discovered that, unlike My-10, the 12.8 antibody binds to baboon stem cells. This difference was of critical importance because it made possible animal studies on baboons which subsequently led to approval of the 12.8 antibody for human use. In addition, the Hutchinson Center scientists developed a system for binding the 12.8 antibody to biotin, a type of vitamin, which was also critical to the subsequent development of a successful product.[2/]

Following their initial work with the 12.8 antibody, Dr. Berenson and others at the Hutchinson Center formed a new company they named CellPro to develop commercial methods of isolating and separating stem cells through use of the 12.8 antibody. The Hutchinson Center granted licenses to CellPro to use the 12.8 antibody and two biotin process patents that had been assigned to it by their inventors. Following additional research, the CellPro scientists perfected a process for purifying stem cells known as the Continuous Flow Immunoadsorption Technique. Using that technique, CellPro's Ceprate SC product has been used successfully to improve bone marrow transplantation in Europe since 1992. In December 1996, the FDA

[2/] The fact that the 12.8 antibody binds with biotin, which in turn binds tightly with avidin, makes possible a process that first separates the stem cells from other cells by binding them to the 12.8 biotin bound antibody, passing them through a column containing avidin, and then separating the stem cells from the 12.8 antibody (which maintains its biotin-avidin bond) by simple agitation. By contrast, the My-10 antibody requires a chemical process to separate the stem cells from the antibody. As a result, work on the My-10 based product has apparently been abandoned and it is questionable whether a My-10 based product will ever be proved safe and effective.

approved Ceprate SC for use in the United States, and the present request is made to ensure that the product will in fact be available in this country.[3/]

II. The Patents at Issue

The patent application filed by Dr. Civin arising out of his My-10 antibody research ultimately led to the issuance of four separate patents. The patents that issued, however, have been held by the district court in the litigation discussed below to have a scope far beyond the My-10 antibody. Indeed, two of the patents have been held by the district court to claim any suspension of human stem cells that is 90% pure or the use of such a suspension in bone marrow transplantation.[4/] The claims of the other two patents relate to antibodies with particular characteristics and methods of isolating stem cells using such antibodies,[5/] but both have been held by the district court to cover the 12.8 antibody or use of CellPro's products in connection with bone marrow transplants.

[3/] Previously, CellPro sold in the United States its Ceprate LC product, a smaller version of the Ceprate SC product that is used in laboratory research.

[4/] U.S. Patent No. 4,965,680 (covering stem cell suspensions and attached hereto as exhibit A) and U.S. Patent No. 5,130,144 (covering transplants using such suspensions) are identical except with regard to the claim language, relevant portions of which are quoted in the court opinion issued in litigation over the patents and attached hereto as exhibit B. How anyone is entitled to a patent on human stem cell suspensions regardless how those suspensions are created -- particularly given the prior "negative" selection work noted in note 1 above -- is one of the issues currently being litigated by CellPro.

[5/] U.S. Patent No. 4,965,204 (antibody) and U.S. Patent No. 5,035,994 (process using antibody), which again are identical except for the claim language quoted by the court. See note 4, supra.

Consistent with the provisions of the Bayh-Dole Act, all of the patents issued to Dr. Civin were assigned to his employer Johns Hopkins, which was the actual grant recipient. Also consistent with Bayh-Dole, each patent recites that the claimed invention "was made with Government support under a grant award from the Department of Health and Human Services" and that "The Government has certain rights in this invention."

Following their issue beginning in 1987, the Civin patents were licensed by Johns Hopkins on an exclusive basis to Becton Dickinson and Company. The terms of that license agreement are unknown to us since Becton Dickinson has declined a request that the protective order governing its use be modified to permit us to review it and to include an analysis of its terms in this request. It is clear, however, that after having worked with the My-10 antibody for several years in an attempt to develop both diagnostic and therapeutic products, Becton Dickinson decided in 1989 to withdraw from the therapeutic end of the business. At that point, under 35 U.S.C. § 202(c)(7)(D), Johns Hopkins should have made reasonable inquiry and if feasible should have given a preference to CellPro or another small business firm for a license of the Civin patents for therapeutic uses.[6/] What happened instead, however, was that Becton

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[6/] The implementing regulations state that if the contractor is a nonprofit organization it "will give a preference to a small business firm when licensing a subject invention if the contractor determines that the small business firm has a plan or proposal for marketing the invention which, if executed, is equally as likely to bring the invention to practical application as any plans or proposals from applicants that are not small business firms; provided that the contractor is also satisfied that the small business firm has the capability and resources to carry out its plan or proposal." 37 C.F.R. § 401.14(k)(4).

Dickinson kept its exclusive license from Johns Hopkins and used it to re-license the Civin patents to Baxter Healthcare Corporation, a unit of a major pharmaceutical firm. Pursuant to an agreement signed in late 1990, Baxter obtained an exclusive license for therapeutic uses (as well as the results of Becton Dickinson's prior efforts in the stem cell field) in exchange for an initial payment of $1,250,000 and a running royalty of 11% on sales of antibodies covered by the patents (or the antibody content of therapeutic products using such antibodies).[7] Although Baxter is a much larger company with far greater resources than CellPro, it has been unable to obtain FDA approval for a stem cell separation product and may never do so. In any event, 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.[8]

III. The CellPro - Baxter Dispute

After obtaining its exclusive re-license from Becton Dickinson, Baxter notified CellPro that Baxter believed the Civin patents covered the 12.8 antibody and its use in purifying

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[7] The terms of the Becton Dickinson to Baxter and Baxter to AIS and Systemix license agreements come from a non-confidential exhibit introduced in the litigation described below and attached hereto as exhibit C.

[8] We understand that Baxter has recently begun development of a product using an antibody other than My-10. This change of antibodies may or may not eventually lead to an approvable product, but it has inevitably set back Baxter's efforts to gain an FDA license.

stem cells for bone marrow transplantation. In early 1992, Baxter wrote to CellPro, offering to license the patents to CellPro on a nonexclusive basis for payment of an up-front fee of $750,000 and a 16% running royalty (representing a 5% markup above the amount it owed Becton Dickinson) on sales of the 12.8 antibody (or the 12.8 antibody content of other products). At or about the same time, Baxter offered nonexclusive licenses to Systemix and Applied Immune Systems, two other companies involved in stem cell research. Eventually, Baxter did enter into nonexclusive license agreements with Systemix and AIS, receiving up front payments of $750,000 from each of them -- thereby more than recouping its own $1.25 million investment -- but neither has subsequently produced a viable product nor paid Baxter more than nominal amounts of running royalties at the rate of 16% specified for sales of the antibody or antibody content of other products.

Although CellPro disagreed with Baxter's assertion that the Civin patents covered the 12.8 antibody discovered by Hutchinson Center scientists and contended that the Civin patents are invalid (particularly if construed as broadly as Baxter contends), CellPro also desired to resolve the matter expeditiously in order to avoid potential disruption to its then-emerging business. Accordingly, CellPro made a counterproposal under which it would have paid Baxter an up-front fee of $500,000, with the fee to be credited against future running royalties that would accrue at a 16% rate on the antibody portion of future CellPro products.[9/]

[9/] In addition, CellPro proposed that the antibody content be capped at 30% of the (continued...)

Baxter rejected CellPro's counteroffer. Instead, it demanded control over CellPro's business in the form of an exclusive right to distribute CellPro products in Europe and Japan where Baxter had no patent rights, as well as a non-exclusive right to distribute CellPro products in the United States.[10/] In CellPro's view, Baxter's new demand was not only unwarranted and unreasonable but also an unlawful attempt to extend the scope of the Civin patents from the United States to foreign countries where they had not and could not be issued. At that point, licensing discussions came to a halt. CellPro sued in federal court in Washington State alleging that the Civin patents were invalid and not infringed by CellPro and seeking relief under the antitrust laws for Baxter's attempt to condition a license of the Civin patents on CellPro's ceding to Baxter exclusive control over CellPro products outside this country.

In September, 1993, CellPro's Washington lawsuit was dismissed for failure to join Johns Hopkins over which there was no personal jurisdiction. Thereafter, Baxter, Becton Dickinson, and Johns Hopkins sued CellPro in Federal court in Delaware, ultimately arguing that CellPro's use of the 12.8 antibody in its Ceprate systems infringes one or more claims of each of

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[9/] (...continued)
total cost of the product. As a result, CellPro would have paid a maximum royalty of 4.8%, an amount that is at the high end of royalty rates for non-exclusive licenses in the biotech area.

[10/] Copies of the relevant correspondence from early in 1992 are attached hereto as exhibit D.

the four Civin patents. At the conclusion of a trial in Delaware in 1995, a jury found the Civin patents were invalid for not enabling their practice and as obvious in light of the prior art. In addition, the jury found that CellPro did not infringe any of the claims of the Civin patents. Thereafter, however, the district court undid the jury verdict on post-trial motions, reinterpreting the primary Civin patent to cover any monoclonal antibody that binds with what the court called "the CD34 antigen." The court then granted Baxter's motion for a new trial, at the same time finding as a matter of law that the patents covering suspensions of stem cells and their use in transplantations were sufficiently enabled by the disclosures contained in them and that by selling the Ceprate product CellPro either infringes those patents or contributes to their infringement by others. The Court of Appeals for the Federal Circuit, which hears appeals in all patent cases, declined to review the district court's rulings on mandamus, noting that "a case may not be appropriate for mandamus 'even though on normal review, a court might find reversible error.'"[11/] A retrial on the remaining issues is scheduled to begin this week.

As would be expected over the course of almost five years of litigation, CellPro and Baxter/Becton Dickinson/Johns Hopkins have attempted to resolve the controversy through settlement and have had recurring licensing discussions. In fact, in an effort to "purge" the attempt to extract exclusive foreign distribution rights that is at the heart of CellPro's antitrust

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11/ In re CellPro, Inc., 99 F.3d 1159 (Fed. Cir. 1996) (citation omitted).

claims against it, Baxter at one point claimed that its original 1992 proposal was still available. When CellPro later offered to accept that proposal, however, it was told it was no longer on the table and that CellPro would have to pay a far greater royalty. Indicative of Baxter's position was the testimony of its "expert" witness at the 1995 trial that a "reasonable royalty" for CellPro's past use of the Civin patents would be an approximately $15 million lump sum payment plus 16% on sales of all CellPro products (not just their antibody content).[12/] More recently Baxter seems to have moderated its view of reasonableness in preparation for the second trial, leading CellPro again to propose a settlement of the controversy. Baxter declined to continue settlement discussions, stating that it expected to prevail on the retrial and that CellPro would then have to withdraw its product from the market.

IV. Request for Exercise of the Government's Rights Under the Bayh-Dole Act

The Bayh-Dole Act was enacted in 1980 "to promote the commercialization and public availability of inventions made in the United States by United States industry and labor." 35 U.S.C. § 200. Previously, patent rights that arose from research funded by federal grants were generally owned by the United States. In enacting Bayh-Dole, Congress made the judgment that policy objectives of commercializing the results of federally-funded research were

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12/ See the exhibit from the first Baxter et al. v. CellPro trial attached hereto as exhibit C.

better served by allowing federal nonprofit grantee institutions like Johns Hopkins to obtain and hold patent rights, with exploitation of inventions generally left to the nonprofits' licensing programs and competitive forces. At the same time, however, Congress recognized that in particular cases the public interest might require government action and therefore included in the Act "march-in" provisions "to ensure that the Government obtains sufficient rights in federally supported inventions to . . . protect the public against nonuse or unreasonable use of inventions." Id. As noted above, the Bayh-Dole Act also contains a policy judgment that small firms should have a preference in obtaining licenses of patents arising out of federally funded research. Id. § 202(c)(7)(D).

To carry out these federal policies, the Bayh-Dole Act provides that a Federal agency may exercise its march-in rights and require the exclusive licensee of an invention made with Federal funds to issue a license to a responsible applicant "upon terms that are reasonable under the circumstances" if the Federal agency determines that

> (a) action is necessary because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use; [or]
>
> (b) action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees."

35 U.S.C. § 203.

In the present instance, both of these statutory bases have plainly been met. Baxter, which has recently announced an intention to sell its division which had unsuccessfully attempted to commercialize the My-10 antibody, "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 process capable of obtaining FDA approval. In contrast, CellPro was granted FDA approval for its Ceprate SC System in December 1996. Also, "action is necessary to alleviate health . . . needs." FDA approval of the Ceprate SC System was based on a clinical trial in bone marrow transplantation for patients with breast cancer. This trial showed that, as compared to traditional bone marrow transplantation, use of the Ceprate SC System reduced toxicities and side effects while maintaining equivalent regeneration of the body's immune system. Other trials designed to establish that the product is safe and effective in treating other forms of cancer or other diseases are underway. The Ceprate System has already been used at over 300 institutions worldwide to treat approximately 5,000 patients. With FDA approval, the lives of many more individuals can be saved or their suffering alleviated with the use of this product.

By its threat to have the Ceprate Systems removed from the market, Baxter proposes to deprive the public in this country -- the public that funded Dr. Civin's research in the first place -- of the benefits of the CellPro product. This, CellPro submits, would plainly violate the statutory mandate that government funded inventions not be used to harm the public through

"nonuse or unreasonable use." Accordingly, there are only two real questions presented by the present request. First, what license terms would be "reasonable under the circumstances," and second, when and how should the agency act.

1. Reasonable Terms Under the Circumstances.

As to the question of reasonable license terms, there are fortunately several clear benchmarks on which the agency can rely. First, Baxter itself initially offered (before attempting to extract exclusive distribution rights over CellPro products) a license based on a lump sum payment of $750,000 and a 16% royalty on antibody sales or the antibody content of other products. Baxter also entered into nonexclusive licenses on essentially these same terms with two competitors of CellPro (though neither of those firms has in fact developed a product). This, CellPro submits, should set a cap on what could be regarded as "reasonable under the circumstances."

In fact, the circumstances -- and the interests of the public which paid for the research that led to the patents and is now being asked to pay again -- cry out for a far lower royalty payment by CellPro. Becton Dickinson originally obtained an exclusive license on the patents (subject of course to the government's march in rights), presumably in exchange for a payment and running royalty, though as noted above it has refused to make available to us the terms of its license agreement with Johns Hopkins. When Becton Dickinson's attempts to use the Civin patents for therapeutic purposes were unsuccessful, Becton Dickinson re-licensed the

patents on an exclusive basis to Baxter for a payment of $1.25 million and a royalty of 11%. These levels of proposed royalty suggest a more reasonable benchmark for a nonexclusive (and thus less valuable) license in the present case. Indeed, had Johns Hopkins complied with the preference in the law for small businesses, Baxter's 1990 license in all likelihood would have gone to CellPro or another small business firm, not Baxter.

Moreover, nothing CellPro has done or will do in the future has benefitted from any proprietary Baxter research or other effort. As noted above, CellPro does not use the My-10 antibody discovered by Dr. Civin. It is only because the patent claims were written broadly and are now claimed to cover other antibodies -- antibodies discovered under federal grant programs at other institutions -- that there is even an issue. To the extent CellPro's product is claimed to infringe, that infringement begins and ends with the work done at Johns Hopkins by Dr. Civin, work funded by the federal grant to which Baxter has no proprietary claim. In fact, CellPro's products use either its own proprietary technology -- research and clinical tests funded by it and its investors -- or technology licensed to CellPro by the Hutchinson Center for which CellPro pays a royalty of 5% of sales (declining to 3% after 10 years) for use of the 12.8 antibody and patents arising out of the Hutchinson Center's federally funded research.

CellPro submits that there may well be reason for the government to adopt regulations covering situations like the present where the same product may be claimed to be covered by patents arising out of work done by more than one federal grantee. Moreover,

investigation may be needed to determine whether the royalty "layering" that plainly exists in the present case -- where federal grantee Johns Hopkins has licensed to Becton Dickinson, which apparently marked up the price and relicensed to Baxter, which in turn clearly marked up the price and relicensed to Systemix and Applied Immune Systems -- is a common problem that leads to unreasonably high royalties (and prices of medical care) that should be dealt with by regulation. But whether or not Baxter is permitted to demand its unearned markup -- a markup CellPro previously indicated to Baxter it was willing to pay because the costs and disruptions of litigation were greater[13/] -- there can be no basis whatever for permitting Baxter to threaten to cause the CellPro product to be withdrawn from the market. Such an act could only be explained as designed either to eliminate a competitor (in the event Baxter's product eventually receives FDA approval) or to punish CellPro for having objected to Baxter's demand to have exclusive distribution rights over CellPro's product and CellPro's decision to contest Baxter's claims of patent infringement and validity. In either event, the public would be improperly deprived of the only available product approved by the FDA.

13/ In March 1994, CellPro sought clarification from Baxter that it could license the patents for a payment of $750,000 and a 16% royalty on antibodies that would be sold separately from the remainder of the product and that it would owe no further royalty to Becton Dickinson. Baxter replied that its offer was no longer on the table and subsequently demanded far greater royalty levels as discussed above.

2. Timing of Agency Action.

As noted above, the patent litigation between Baxter and CellPro is continuing with a retrial scheduled to begin this week. CellPro has been hopeful that a second jury would rule the same way the first one did, eliminating any claim that its products infringe the Civin patents. The district court's more recent post-trial rulings have substantially limited CellPro's arguments and have largely precluded that outcome. Even were it to lose at the second trial, however, CellPro believes that the Federal Circuit should and would reverse the district court and re-enter the initial jury's verdict.

Under these circumstances, the present request might ordinarily be regarded as premature, since the action sought might never be needed. Unfortunately, however, the time periods set forth to govern the government's exercise of its "march in" rights under the regulations promulgated under Bayh-Dole are such that awaiting the outcome of the forthcoming trial and any resulting appeal is not a viable possibility. Baxter's counsel stated at a pre-trial hearing last week that Baxter intends to seek a permanent injunction to have CellPro's products removed from the market if it prevails in the retrial. To delay agency consideration of this application until that litigation has terminated would inevitably preclude the granting of needed relief for many months. Moreover, Baxter's continuing threat has created great uncertainty both in the minds of investors who need to provide funds to enable CellPro to increase production of its now-FDA approved product and must consider the impact on CellPro inherent in Baxter's threat and in the minds of doctors and their patients when they consider

embarking on a course of treatment that would involve the use of a product that might end up not being available.

Because waiting is not a viable option, CellPro respectfully asks that the agency immediately initiate the procedures set forth in 37 C.F.R. § 401.6 and upon the conclusion of those procedures provide it the march in rights required under the circumstances to avoid harm to the public interest.

V. Conclusion

Baxter has threatened to require CellPro to remove the Ceprate products from the market on the basis of patents issued to Johns Hopkins that are governed by the Bayh-Dole Act. In doing so, Baxter threatens the welfare and very lives of many individuals who need bone marrow transplants and whose suffering could be lessened and whose lives could be saved with these products. The Secretary has the authority under the applicable law and regulations to avoid this result, and on behalf of CellPro, we urge that you take immediate steps to do so. We would also appreciate the opportunity to meet and discuss this request with Health and Human Services and NIH staff at the earliest possible opportunity.

Very truly yours,

Lloyd N. Cutler

Birch Bayh

cc: Harriet Rabb
Robert Lanman