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July 30, 1997

Barbara M. McGarey
Deputy Director
Office of Technology Transfer
National Institutes of Health
6011 Executive Blvd.
Suite 325
Rockville, MD 20852

Re: Petition of CellPro, Inc.

Dear Ms. McGarey:

Earlier today, I received a copy of the July 28, 1997 issue of BioCentury, which contains an article on the CellPro litigation. I enclose a copy for your information, since it may come to the attention of you or others at NIH sometime in the future.

Much to my dismay, the article attributes to me a prediction about the outcome of the NIH's review of CellPro's march-in petition. I made no such statement to the reporter.

After reading the article, I telephoned the reporter, Karen Bernstein. After reviewing her notes of her interview with me, she confirmed that I was right and that I had made no prediction of what action NIH would take. My statement to her was only that on August 4, NIH might deny CellPro's petition or it might initiate a formal administrative proceeding.

Ms. Bernstein was most apologetic and assured me that she would publish a correction in next week's issue. She also said that she would be happy to confirm her mistake by telephone with anyone who wishes to call her prior to publication of the correction. Her telephone number is (415) 595-5333.

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I am hopeful that Ms. Bernstein's mistake will not cause NIH any embarrassment.

Sincerely yours,

Donald R. Ware

DRW/kaw

Enclosure

cc: Robert B. Lanman, Esq.
Gary D. Wilson, Esq.

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Noteworthy

Judge hammers CellPro

By Karen Bernstein
Editor-In-Chief

CellPro Inc. came two steps closer last week to losing the market for its Ceprate SC Stem Cell Concentration System, as an FDA advisory panel recommended approval of rival Baxter Healthcare Corp.'s Isolex 300 Magnetic Cell Separator System, and a federal court judge granted an injunction against sales of Ceprate once Isolex is approved.

In a sharply worded ruling, Judge Roderick McKelvie of the U.S. District Court in Wilmington, Del., ordered CPRO to pay Johns Hopkins University, Becton Dickinson & Co. and Baxter treble damages of $7 million for willful infringement of the plaintiffs' patents involving CD34+ stem cell selection technology. He also entered an injunction against sales of Ceprate after Isolex is approved by the FDA *(see BioCentury Extra, July 25)*.

In March, a jury found that CPRO infringed two patents (the "Civin" patents, Nos. 4,714,680 and 4,965,204) covering CD34 monoclonal antibodies and purified stem cells and awarded the plaintiffs $2.3 million in damages *(see BioCentury March 10 and March 17)*.

In his ruling, the judge wrote that "behind the science, the medicine, and the potential for treating cancer patients are investors who have demonstrated that their primary motivation is not humanitarianism, nor even responsible capitalism. The record in this case demonstrates that CellPro's motivation, as expressed by the words, conduct, and testimony of its founders, is greed. They are prepared to stretch the boundaries of marketplace competition to maximize their returns. They will deliberately take what is not theirs, pad their files and financial disclosures with weak and misleading opinions of counsel, and litigate to delay and frustrate."

McKelvie wrote that the award, the maximum allowable, "is an appropriate amount to punish CellPro for its deliberate and bad-faith infringement of the Civin patents."

McKelvie noted that, while CPRO had initially claimed that the Johns Hopkins patents were invalid based on obviousness and prior art, during the trial the company dropped that defense. Instead, the judge wrote, the company focused its defense on lack of enablement of the Civin patents.

Under the ruling, CPRO will be allowed to continue U.S. sales pending approval of Isolex, and for three months following approval, provided that it gives 60 percent of the profits to the plaintiffs. "The judge's rationale," said Donald Ware, an attorney for the plaintiffs from the Boston law firm Foley, Hoag & Eliot, "was that CellPro needs to retain some profit to have sufficient incentive to stay in the business, but he couldn't ignore the fact that CellPro has been found to be infringing."

Outside the U.S., CPRO will be allowed to sell Ceprate for one year, provided sales do not exceed the level sold in the last quarter of 1996. Although CPRO hasn't broken out numbers, the company posted revenues of $9.5 million in the fiscal year ended March 31 and $3.1 million for the fourth quarter, of which the majority were European sales. Sales for the quarter ended Dec. 31, 1996 were $2.5 million.

The judge's order also requires that CPRO decrease sales outside the U.S. in 25 percent increments each quarter. CPRO will have to pay the plaintiffs 60 percent of European profits as

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Europe

EC blinks on GMOs

The European Commission (EC) has backed off from threats by Agriculture Commissioner Franz Fischler that Europe would require segregation of agricultural commodities containing or derived from genetically modified organisms.

The Commission, which has been under public pressure by U.S. officials to abandon the segregation proposal *(see BioCentury, June 23)*, last week said that it will develop legislation that "will be consistent with the European Union's international obligations and which does not impose mandatory segregation of production, transport and distribution" of products.

The Commission statement indicated that it has "agreed on a general orientation on the labeling of products produced from genetically modified organisms (GMOs), intended to ensure a coherent European Union approach across the different sectors regulating the use of GMOs in the food chain. On the basis of this approach, the Commission will propose measures which will cover all products placed on the market following the safety approval, both 'live' GMOs and products derived from GMOs, thus guaranteeing coherent labeling throughout the production chain."

The approach would lead to three labeling options: voluntary labeling ("this does not contain . . . ") for certified non-GMO produce; mandatory labelling ("this contains . . . ") for produce known to be of GMO origin; and mandatory labeling ("this may contain . . .") in cases where material of GMO origin cannot be excluded but where no evidence of the presence of such material is available.

The Commission stated that labeling should "give consumers clear, honest and neutral information about the GMO origin of products, facilitating choice for consumers without stigmatising modern biotechnology or raising doubts about the safety of products."

The commission said the labelling requirements should cover as many products as possible where reliable scientific tests exist to prove a GMO origin. In cases where no agreed scientific verification of a GMO exists, the commission called for voluntarily cooperation by industry.

Among other things, the commission intends to present specific initiatives covering animal feeds and seeds in the course of 1997.

— Steve Usdin

Noteworthy

Hybridon abandons antisense trial

By Ilan Zipkin
Staff Writer

Hybridon Inc. on Friday said it has stopped development of its GEM91 phosphorothioate antisense oligonucleotide for treatment of HIV/AIDS, citing side effect and efficacy problems it hopes will be overcome with second-generation compounds. HYBN was down $1.625 Friday, closing the week at $3.125.

The decision came after HYBN's open label Phase II trial was halted based on analysis of data from 9 of an expected 12 patients with advanced AIDS. The patients had received 3.2 mg/kg/day of GEM91 by iv for 14 days. After 10 days of therapy, 3 of the 9 had to discontinue treatment when their platelet counts dropped below 50,000 platelets/mm³. Also, decreased levels of infectious virus seen in earlier trials were not observed in this study.

Based on these inconsistent efficacy data, HYBN (Cambridge, Mass.) concluded that the dose-limiting need to suspend treatment if platelet counts fell prohibited use of the compound in an AIDS setting, where sustained treatment is essential to prevent the emergence of viral resistance.

HYBN Chairman and CEO E. Andrews Grinstead said "we had a responsibility to use first-generation compounds as long as there was utility for them. But in the face of these results, it made sense to move on to second generation."

Previous Phase I/II trials of GEM91 in a total of 120 AIDS patients tested doses of up to 4.4 mg/kg/day, but only for 8 days of therapy. Russell Martin, VP of drug development, said that treated patients showed a 0.7 log drop in HIV levels more frequently than placebo in the earlier trials. In patients with advanced AIDS, this drop was as high as 1.3 logs.

Martin said that platelet effects were seen in the Phase I/II trial beginning at a dose of 2 mg/kg/day, but that the platelet counts recovered, and the effect did not seem to get worse with higher doses. HYBN had hoped that the current trial would confirm these preliminary virology and safety data.

However, Martin said, "it's a regular feature with first generation phosphorothioate compounds to see platelet effects." He said that the negative charge of the oligo could have general effects, and that sequence-specific effects of GM91 were possible as well.

Martin suggested that platelets may have been sequestered by increased binding to endothelial cells, but that no thrombosis or suppression of marrow was seen.

As for the inconsistency seen with viral levels, Martin said that "longer-term treatment may be necessary to show the full effect of antisense compounds."

HYBN now intends to focus development on second-generation compounds, "mixed backbone" oligos that contain segments of both RNA and DNA, as well as other substitutions designed to reduce the ionic charge of the molecule.

These oligos are intended to solve several of the problems presented by phosphorothioate oligos. First, they are expected to be delivered orally, allowing for better compliance and long-term dosing. Second, they seem to be more stable, allowing lower dosing. Most importantly, Martin said, they are not limited by platelet effects or liver toxicity, allowing treatment to continue over a longer term.

Along with GEM92, HYBN is working on three other second-generation antisense compounds. GEM132 is in Phase II trials for systemic CMV infection and retinitis. GEM231, directed against protein kinase A, is expected to enter colon cancer trials in the fourth quarter. GEM220, which targets VEGF (vascular endothelial growth factor), is scheduled to enter the clinic in early 1998 to treat retinopathies, psoriasis, or solid tumors.

Grinstead said that HYBN "will conserve our resources now that we have a serious question about the first generation product." With $45 million in cash and a $5 million per month burn rate at the end of the first quarter, Grinstead expects that some of HYBN's 201 employees could be laid off.

After the disappointing clinical news, HYBN withdrew its shelf registration for an offering of 5 million shares (see *Offerings*, *B14*). HYBN has 25 million shares outstanding.

CellPro,
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well, Ware said. Isolex already is sold in Europe.

The judge rejected CPRO's request to stay his order pending an appeal. CPRO has filed a notice of appeal with the District Court to stay the injunction pending an appeal to the Court of Appeals for the Federal Circuit, said CPRO President and CEO Richard Murdock.

Also pending, with an initial decision likely to be made by Aug. 4, is CPRO's petition to the U.S. Department of Health and Human Services that the agency provide CPRO with a compulsory license to the Civin patents.

According to Murdock, the National Institutes of Health, to which HHS has delegated the decision, could do one of three things: order Johns Hopkins to license the patents to CPRO, deny the petition, or initiate formal proceedings to take evidence. Both Ware and Murdock think the third alternative is most likely.

If the worst case scenario occurs and the court's verdict is upheld and NIH denies CPRO's petition, the company is in trouble. "If we can't find a business solution and we come off the market, that would have a pretty detrimental effect on the company," Murdock said. "It is unlikely we could survive or survive in the same form as today."

The company has other products in development, including systems to produce dendritic cell vaccines, and cell separation for cell populations besides CD34+ cells, including T cell subsets. But all are in earlier development, Murdock noted.

The company's T cell depletion device has been approved in Europe and is in development in the U.S. The next products likely to enter the marketplace are CD4 and CD8 T cell subsets, which CPRO hopes to have available in Europe in 1998.

The company's lymphoma purging system is entering the clinic soon, and both the breast cancer purging column and the ex vivo dendritic cell vaccine are expected to enter the clinic this year.

The company had $54 million in cash at March 31 and is burning $22-$23 million a year.

CPRO's shares edged down $0.125 to $4.50 on the week.