ISHAGE Telegraft

Vol. 4, No. 1 — February, 1997

FDA APPROVES 1ST STEM CELL SELECTION DEVICE

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Background

A decade ago, most experimental hematologists thought that hematopoietic stem cells (HSC) were too elusive and rare to be isolated, let alone used clinically. ISHAGE had yet to be incorporated and its founders had no idea that they would be devoting a large portion of every meeting of the newly created Society to issues involving CD34+ stem cells. Even the suggestion that one could identify or characterize a population of blood cells capable of long term renewal sparked many heated debates.

In the same period, several researchers developed monoclonal antibodies to a marker found on cells capable of generating *in vitro* hematopoietic colonies (later termed CD34) and cautiously suggested that a subset of these 'CD34-bearing' cells were actually the long sought-after HSC.

By the late 1980's, a young oncologist in Seattle believed that enough pieces of the puzzle had been assembled, through his own research and that of others, to go forward with the development of a clinical device that could purify these stem cells in large enough quantities for bone marrow transplantation (BMT). Dr. Ronald Berenson, in founding CellPro Inc., knew that it would require considerable capital, a network of clinical investigators and scientists on an international level, and considerable faith in his principles to achieve this goal.

Many of his colleagues were investigating HSC by negative selection techniques. In contrast, he first incubated marrow cells with biotinylated anti-CD34 monoclonal antibodies and then captured the HSC by passing these cells over an avidin bead column. Dr. Berenson was able to 'positively select' out the CD34+ cells; mild agitation was then used to disrupt the cell/antibody bond allowing the collection of a purified cell population.

He also had the foresight to involve biomaterial engineers from the beginning to translate the small scale research devices into large scale, using friendly, closed clinical systems which could efficiently process whole marrow or peripheral blood stem cell (PBSC) harvests. His dream was realized on December 6, 1996 when, after 5 years of intense clinical development, the FDA granted marketing approval for the CEPRATE® SC Stem Cell Concentrator. Prior to this announcement, the device had already received both the European CE mark and ISO 9002 quality certification.

Corporate Impact

Like many biotech companies, CellPro Inc. has reported an overall financial loss since its incorporation. For the past 5 years, its core technology could only be used in conjunction with FDA approved clinical trials. After delaying approval in 1995, the FDA did allow CellPro to institute a limited cost recovery program to recoup some of their manufacturing costs for the columns.

The company is now in the process of making the transition from a primarily R&D based philosophy to one focused on marketing and increased production. Dr. Berenson, then Vice President of Research and Development, left CellPro in 1995, while Rick Murdock, CEO, remained to execute the transition.

Also like many other biotech companies, CellPro's financial resources have been drained by ongoing litigation. CellPro is the defendant in a patent infringement suit filed by Baxter Healthcare, Becton Dickinson and the Johns Hopkins University over the CEPRATE® technology. While the jury trial ending in August 1995 concluded that there was no patent infringement by CellPro, a retrial was later ordered for early March, 1997.

Clinical Impact

During the past 5 years, the field of hematopoietic cell therapy has changed dramatically. It must be remembered

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that only recently has ISHAGE reached a consensus on the quantitation of $CD34^+$ cells, or actually approved Standards for HSC processing. It had become apparent early on that the field was advancing at an accelerated pace: bone marrow - long considered the only true stem cell source- was being supplanted, in many instances by PBSC products.

Unfortunately, the U.S. regulatory process for biologics has only recently improved its efficiency. Therefore, CellPro and the FDA were committed to a trial that would have less clinical impact than was originally expected. The experimental arm of this phase III randomized trial in advanced breast cancer investigated the ability of $CD34^+$ selected marrow to reduce the infusional toxicities (by virtue of its smaller volumes and cell numbers) of cryopreserved marrow without compromising engraftment.

During the same time period, most of the principal investigator sponsored studies (IDE's) using $CD34^+$ selection devices employed PBSC or allogeneic marrow as the source of $CD34^+$ cells. It should be noted, however, that until trilineage engraftment was demonstrated first in primates and later in the first phase I/II trials using $CD34^+$ selected marrow, no one was absolutely certain that these positively selected cells contained the elusive stem cells. By the time of the final FDA review in February, 1996, most of the trial's conclusions seemed inconsequential compared to the large amount of promising data being generated on other investigational studies using this and other corporations' stem cell selection devices. The CEPRATE® device was also being marketed in Europe and Canada.

Thus, in making the unanimous recommendation for approval, the FDA's Biological Response Modifiers Advisory Committee emphasized that the device should be approved based on its future potential in gene therapy, tumor cell purging, and use with alternative stem cell sources in addition to the study that lay before them. This was a milestone in the field of hematotherapy, but also posed serious questions related to the designs used for future graft engineering trials.

Impact on the Field

CellPro Inc. is currently selling the disposable CEPRATE® kits for $4,325.00 US, while the computerized $CD34^+$ selection system can be purchased for slightly under $25,000 or leased through various contract arrangements.

The approved indication is in autologous BMT. There is a high probability that this indication will be under-utilized.

Off-label use by physicians (which is not regulated by the FDA in a manner similar to investigational devices) will probably account for the majority of sales in the US. Many devices will undoubtedly be used in conjunction with cooperative (ECOG, SWOG, POG etc.) or corporate PBSC trials.

Outside of these settings, they will be closely scrutinized by health care provider organizations and the native institution. Discussions with the FDA suggest that most IDEs submitted for $CD34^+$ selection of autologous marrow of PBSC will receive little or no scrutiny. However the FDA will probably concentrate on the efficacy and safety of those $CD34^+$ selection protocols utilizing allogeneic or unrelated marrow, PBSC or cord blood as the stem cell source.

Significant advances have already been made on several investigational studies using $CD34^+$ selection for T cell depletion in allogeneic, unrelated and *in utero* BMT, tumor cell purging and ex-vivo expansion of PBSC harvests and in providing enriched stem cell preparations for gene therapy.

CellPro has also expanded its positive selection core technology. Clinical trials are underway using a new column which further depletes T cells from allogeneic PBSC grafts to reduce the incidence of GVHD. Both CD4 and CD8 columns are also entering preclinical investigation for post-transplant immunotherapy applications. The eventual offerings for positive selection are limited only by the number of antigenic determinants. Combination with negative selection is also feasible.

The FDA, CellPro, and the many investigators conducting the $CD34^+$ selection trials should take satisfaction in knowing that they have significantly advanced the field of hematotherapy and helped to lay the ground work for its future regulation and development.

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