AASTROM BIOSCIENCES, INC.

A Patient-Friendly Approach to Human Cell Transplantation

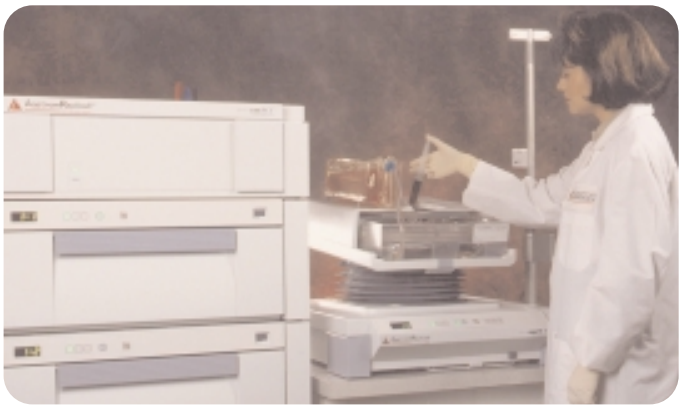
One of the most important recent developments in cancer treatment has been the ability to harvest stem cells from bone marrow or blood to produce blood and immune system cells, and inject them into a cancer patient after drug or radiation therapy. These therapies kill cancer cells, but they also destroy life-protecting stem cells. Reinfusion of harvested stem cells enables the body to regenerate the blood and immune systems in the now cancer-free patient. Preferably, the stem cells come from the patient's own bone marrow. When that is not feasible, they may be taken from another donor.

COMPOSITE PERFORMANCE SCORE
(Based on a four star rating.)
★ ★ ★ ★

Serious Drawbacks to Existing Methods

Good as it is, stem cell harvesting has important drawbacks. Harvesting stem cells from bone marrow is painful, usually requiring 100 to 140 needle sticks — performed as major surgery under general anesthesia — to extract from the hip or other large bones enough marrow for successful transplantation. Some cancer patients are not strong enough to withstand so many extractions. A few are so ill they can't afford to postpone therapy while stem cells are being harvested. Still others suffer significant side effects (pneumonia, pulmonary embolism, bone marrow inflammation) from the extraction process itself. A typical procedure involves eight separate donor visits (one for the extraction, several for blood testing and other medical procedures, one for reinfusion of the stem cells), takes about 16 hours altogether and costs $10,000 to $15,000.

...the cell expansion system...could eventually mitigate most of the drawbacks associated with current harvesting techniques while reducing costs and increasing the number of patients who could use Aastrom's procedure.



Ex Vivo cell expansion—from lab to the clinic.

Another harvesting method — peripheral blood progenitor cell (PBPC) collection — is in some ways an improvement over traditional bone marrow harvesting. PBPC involves injecting the donor (who might be the patient) with drugs to stimulate the movement of stem cells from the bone marrow into the blood stream. When it becomes enriched with stem cells, the blood is circulated through an apheresis machine, where stem cells are separated, and then back to the donor.

PBPC collection typically involves 21 donor visits (at least one for drug administration, three or four for apheresis, some for blood work, others for follow-up work related to the apheresis, one for reinfusion); takes an average of 39 total hours; requires about 22 needle sticks; and costs around $16,000. It has gained popularity over bone marrow

harvesting in recent years, the company reports. This is particularly true for collecting cells from cancer patients themselves, in part because some patients receiving PBPC-based treatment have less need for platelet transfusion.

The overall costs of cancer treatment where stem cell therapy is used may total $100,000 or more. These costs include diagnosis, chemotherapy, radiation therapy, stem cell transplant therapy, and patient management. The costs of stem cell transplant therapy include the costs of cell collection, the costs of reinfusing the cells, and patient support during post-transplant recovery. The latter involves hospitalization, antibiotic treatment, infusions of platelets and red blood cells, and management of adverse reactions to large-volume cell infusions.

Injecting Into Processor.

New Approach Promises Large Benefits

A cell expansion system developed by Aastrom Biosciences could potentially mitigate most of the drawbacks associated with current harvesting techniques while reducing costs and increasing the number of patients who could use Aastrom's procedure. The company was founded in 1989 and had only four persons on staff when it gained ATP support three years later. Wide-scale use of its system would produce large benefits across the economy via new therapies, reduced treatment costs and lower risks to patients undergoing cell harvesting and transplantation.

Aastrom's policy is to disseminate its findings widely after establishing protections for its intellectual property.

Aastrom expects cell harvesting via its Aastrom-Replicell™ Cell Production System — which induces cells to rapidly multiply or expand — will be cost competitive. The typical patient/donor is likely to need just two clinic visits, one for harvesting a small amount of bone marrow and the other for reinfusing the expanded cells. An average of just seven needle sticks would be required during the initial visit.

The core technology of the system is a bioreactor that expands small amounts of bone marrow into a transplant product rich in stem cells and progenitor cells (stem cells that have started maturing into blood or immune cells). During a single 20-minute outpatient procedure, less than 50 millimeters of bone marrow is extracted from the patient under local anesthesia. The marrow is injected into a disposable cassette — about the size of a large pizza — which is inserted like a video cassette into the automated bioreactor. A key aspect of the system is the creation of culture conditions that duplicate the human bone marrow environment. The cassette uses growth media, oxygen supplies, and proprietary processes within the bioreactor to stimulate the marrow to produce its own growth factors. Over 12 days, the cell population expands 5 to 10 times while stem and progenitor cells expand even more, producing enough cells for effective transplantation.

Another clinical trial, completed in May 1997, reported excellent findings for six breast cancer patients...

Scale-Up and Clinical Trials

Aastrom has successfully scaled up a small laboratory prototype of the cell expansion system to one large enough for clinical use. Clinical research has confirmed that cells produced by this device, called "the System," can safely be infused into patients.

In the first test of the System, a dose-ranging study with seven lymphoma patients at the University of Michigan Medical Center in 1993, Aastrom found that stem cells generated with its procedure were as safe as those collected by the direct bone-marrow harvesting technique. And in the first feasibility trial of the System — with 10 breast cancer patients at the University of Texas M.D. Anderson Cancer Center in Houston — standard clinical recoveries were seen following injection of the System-produced cells, showing that the System can be operated adequately by clinical personnel.

Another clinical trial, completed in May 1997, reported excellent findings for six breast cancer patients treated through the Bone Marrow Transplant Program at Loyola University Medical Center in Chicago. The study demonstrated that the System technique produced recovery results in line with outcomes for transplantation using other cell harvesting procedures.

Favorable results were also reported at the American Society of Hematology conference in December 1997. A Duke

PROJECT HIGHLIGHTS

PROJECT:
To design and construct a desktop-size device that can expand small samples of stem cells, a process that would enable reductions in the risk, pain, time and cost of collecting these specialized blood-production cells for use in bone marrow transplantation for cancer patients.

Duration: 7/1/1992 — 6/30/1994

ATP Number: 91-01-0243

FUNDING (in thousands):

ATP	$1,220	45%
Company	1,514	55%
Total	$2,734	

ACCOMPLISHMENTS:
Aastrom designed, constructed and validated a desktop-size bioreactor to produce large amounts of stem and other cells from bone marrow, umbilical cord blood and possibly other human tissues. A number of signs indicate the value of this accomplishment:

- Aastrom received a fundamental patent for its bioreactor: "Bioreactor for Mammalian Cell Growth and Maintenance" (No. 5,688,687: filed 6/7/1995, granted 11/18/1997).
- It has applied for several additional patents for technologies related to the ATP project.
- By the end of the ATP award period in June 1994, Aastrom staff had published or presented at professional conferences numerous technical papers on the company's Aastrom-ReplicellTM Cell Production System (System), which incorporates the Biochamber developed with ATP funds.
- In October 1995, Aastrom received $35 million from Rhone-Poulenc Rorer for use of System technology worldwide for cell and gene therapies involving lymphoid blood cells.
- Aastrom raised $21 million in new investment capital via an initial public stock offering in February 1997.
- In November 1997, when Aastrom received the patent listed above, the company's stock price jumped more than 60 percent in one day.
- By the end of 1997, Aastrom had entered into agreements with SeaMED and Ethox Corporations and Anchor Advanced Products for the collaborative development and manufacture of certain components of the system.
- To date, the System has been used in clinical trials at six U.S. and two foreign sites with more than 60 patients, and additional trials are underway.

COMMERCIALIZATION STATUS:
Clinical trials are in progress. The firm is also looking for partners with whom to develop a marketing relationship.

OUTLOOK:
There are high expectations that this new technology will be useful in a variety of medical treatments. Test results at various stages in the regulatory process have been promising. The stock market response to the initial public stock offering, patent-grant announcements and attention from investment analysts suggest that the private market believes the company and its technology have a good future. Also, a recent detailed economic study indicates this new technological approach could yield significant social benefits just in treating cancer patients with solid tumors.

Composite Performance Score: ★ ★ ★ ★

COMPANY:
Aastrom Biosciences, Inc.
Dominos Farms, Lobby L
24 Frank Lloyd Wright Drive
Ann Arbor, MI 48106

Contact: Alan K. Smith

Phone: (734) 930-5555

Number of employees: 4 at project start, 70 at the end of 1997

University Medical Center preclinical study showed that the System reduced the number of tumor cells during production. At the same conference, Aastrom announced completion of another Loyola clinical study, this one with 19 patients, that generated further evidence that bone marrow grown in the System retained stem and other key immune cells needed to restore vital tissues after drug and radiation therapy.

Intellectual Property and Stock Market Reaction

Protection of its intellectual property has always been important to Aastrom. The company was founded as a joint effort between the company's initial investors and the University of Michigan. The investors and the university agreed that inventions by the three principal researchers, all university professors, would be assigned to the university and licensed exclusively to Aastrom. In March 1992, prior to the ATP award, Aastrom and the university signed a detailed licensing and royalty agreement. Through the end of 1997, 12 patents covered by the agreement had come out of the Aastrom/University of Michigan collaboration. Most of them underlay the ATP-funded technology. News reports about the granting of two of them in September 1997 were immediately followed by a substantial increase in the price of the company's stock.

The company is also pursuing patent protection for inventions not covered by the agreement with the university. In 1997, Aastrom received in its own name a fundamental patent — "Bioreactor for Mammalian Cell Growth and Maintenance" — for the System method and device. News that this patent had been granted was accompanied by a one-day increase of 60 percent in the company's stock price.

Aastrom's policy is to disseminate its findings widely after establishing protections for its intellectual property. This is true of the technical specifics of its discoveries, as

well as the results of clinical trials. Company staff have produced numerous papers for presentation at professional conferences or publication in professional journals.

Strategic Alliances for Commercialization

In 1993, the company entered into a strategic alliance with COBE Laboratories and COBE BCT (collectively, COBE) for the worldwide distribution of the System for stem cell therapy and related uses. COBE committed up to $20 million in equity investment in Aastrom. In addition, Aastrom and COBE initiated a clinical trial in France in early 1997 to evaluate the use of System cells to promote the recovery of blood cell production in breast cancer patients undergoing aggressive marrow-damaging chemotherapy. Aastrom is seeking approval to market the System in Europe.

Other possible applications include immunotherapy, stem cell gene therapy and cells for solid tissue repair.

In September 1995, Aastrom entered into a research and development collaboration with Rhone-Poulenc Rorer (RPR), granting RPR a right to license the System for lymphoid cell applications. Under the agreement, RPR will invest $35 million. In September 1997, Aastrom had received $3.5 million in equity payments and $1.5 million in revenues from RPR.

Initial Public Stock Offering

In addition to financial support from strategic alliances, the company has secured funding in the public capital market. In February 1997, Aastrom conducted its initial public stock offering, which raised $21 million, and conducted another offering in December 1997 that raised $11 million.

All equity funding is invested in Aastrom's research and development (R&D) efforts and administrative activities required to support that research — the only focus of the company's activities. Thus, as Aastrom succeeded in attracting more private capital, ATP funding constituted a declining proportion of its R&D spending. ATP funds amounted to 23 percent of Aastrom's $2.6 million R&D budget in 1993 but only 11 percent of its $4.9 million R&D budget in 1994.

Aastrom does not manufacture products, nor does it intend to. It arranges with third parties to manufacture its candidate products and has agreements with SeaMED and Ethox Corporations and Anchor Advanced Products, Mid-State Plastics Division, for the collaborative development and manufacture of certain components of the Aastrom-Replicell™ System.

Inserting Cell Cassette into Incubator.

Large Potential Benefits

Patients — the main beneficiaries of the new technology — are expected to gain from a less invasive procedure that is cost effective, provides greater procedural flexibility, and offers tumor purging benefits. In addition, because of fewer hospital or clinic visits, total costs are expected to be as much as 25 percent less ($12,000 instead of $16,000) than costs for PBPC apheresis. Furthermore, if the Aastrom technology substantially decreases the cost of cell transplantation, others who could not have afforded the treatment will now be able to and will benefit. Their benefit may well be life itself, since bone marrow transplantation for cancer patients is frequently a life-saving therapy.

A study of tissue engineering projects, conducted by economists at Research Triangle Institute, Inc. (RTI), under contract to the ATP, noted that Aastrom achieved ATP-project results one to two years earlier than would have been possible without the ATP award. Having the ATP funds also helped the company attract additional equity capital and establish new strategic partnerships. These, in turn, helped accelerate the company's R&D even more.

Wide-scale use of the System is expected to produce large benefits across the economy via reduced treatment costs and lower risks to patients undergoing cell harvesting and transplantation. The RTI study estimates that the present value of expected net benefits from using the System technology for just one type of application — treating cancer patients with solid tumors — exceeds $100 million. The study estimates that ATP's contribution of $1.5 million to the project will generate nearly $50 million of the expected benefits by speeding the technology's development by one to two years. The RTI study did not attempt to develop estimates based on characteristics of System-based stem cell transplantation that might yield better patient outcomes. It focused only on cost savings.

In addition, the study did not attempt to estimate the value of the effects that a number of other potential appli-

cations might have. First use of the System technology is for expanding small amounts of stem cells from bone marrow. It has now been extended to the production of stem cells from umbilical cord blood. Other possible applications include immunotherapy, stem cell gene therapy and cells for solid tissue repair. More benefits can be expected to be generated as the company applies the technology to growing other types of cells — platelets and red blood cells, as well as liver, kidney and nerve tissue — outside the body.