



## Pluristem Aims to Replace Bone Marrow Transplants

### *Invention Based on Mimicking Natural Bone Marrow*



An estimated 100,000 leukemia and other patients die each year because of difficulties encountered in obtaining a bone marrow transplant. Many are unable to find a suitable donor while others undergo transplants that fail because of complications. A new technology developed by Haifa-based startup Pluristem Life Systems offers a way to restore patients with healthy blood-producing cells without having them actually undergo a bone marrow transplant.

The Pluristem invention does so by leveraging a breakthrough that has already taken place in the treatment of child patients requiring bone marrow transplants.

In recent years health organizations have created banks of frozen umbilical cord blood, derived from umbilical cords discarded after birth. Umbilical cord blood enables more flexible tissue matching than bone marrow because there are fewer differences among the less mature cord blood stem cells.

“The odds of finding a tissue match drop dramatically from one in 6 million when bone marrow is used to one in 10,000 when a search is conducted in umbilical cord blood banks, says CEO Zami Aberman, the CEO of Pluristem, (PLRS:OB). He points out that a supply possibly already exists for every patient who needs a transplant, aided in part by the establishment of a national cord blood bank in the US brought into existence by a \$79 million bill signed by President Bush.

“There are already several hundred thousand umbilical cord units in public banks which should be enough to provide a match for any patient requiring a transplant. But there are several obstacles that stand in the way of making this a universal solution. The first problem is that there usually aren't enough blood-producing stem cells in the cord blood. The blood from an average baby's umbilical cord usually provides less than a third of the amount needed for the average adult patient. The second problem is the relatively late engraftment of cord blood cells compared to bone marrow-derived cells. This can result in the rejection of the engrafted tissue (Graft versus Host disease) as well as in other complications. There also are problems when there is a slow rate of recovery,” he explains.

In a standard bone marrow transplant the patient requires about 170,000 hematopoietic stem cells (hscHSC) for every kilogram of body weight. As adult patients typically require more than 12 million cells and portions of umbilical cord blood seldom contain more than 4-5 million hemopoietic stem cells, umbilical cord blood transplants may usually only be carried out on children. Indeed of the approximate 6,000 umbilical cord blood stem cell transplants that have been carried out to date, the majority have been child patients who require smaller amounts of blood.

Pluristem's PLX 1 is a new approach that aims to improve and speed up the engraftment of the HSC from cord blood transplanted cells in both adult and child patients.

PLX-1 is one of a series of innovative Pluristem technologies based on the company's core technology -- a bioreactor that simulates natural bone marrow.

“We try to create an environment that is as close as possible to nature and that mimics natural physiological conditions without adding any non-natural substances,” says Dr. Ora Berger, Head of R&D. “Then we let good things happen.”

The good things that happen in Pluristem's natural bone marrow environment with PLX-1, Dr. Berger points out, are quite dramatic.

PLX-1 is based on supplementing the umbilical cord blood cells with mesenchymal stroma cells (MSC). MSC build bone marrow and other human tissues and create the conditions that enable hematopoiesis, the process by which new blood cells are created. PLX-1 is based on growing MSC in an environment that simulates the natural three dimensional environment of bone marrow. MSC can be derived from placentas and are readily available without any ethical problems.

In recent pre-clinical trials Pluristem showed that the PLX-1 technology could be highly effective. Pluristem demonstrated that when immune-deficient NOD/SCID mice were injected with umbilical cord blood stem cells along with PLX-1 cells the capacity of the animals to engraft stem cells increased three fold in comparison to a control group which was injected with umbilical cord blood but without PLX-1.

“The significance of the trial is that we have shown that sufficient engraftment is possible with the limited number of hemopoietic stem cells available in a single portion of umbilical cord blood,” said Aberman. “This paves the way towards using umbilical cord blood instead of bone marrow transplants for adult patients as well as improving the effectiveness of engraftments in child patients and shortening recovery times.”

“If we can successfully duplicate this achievement in human patients, the door will be open to treating more than 100,000 patients a year this way,” he adds, pointing out that this would comprise a multi-million dollar market.

Aberman points out that Pluristem’s system offers several advantages over other competing technologies which are being developed to increase the number of HSC’s in umbilical cord blood.

One of these is ex-vivo expansion, a system whereby an attempt is made to increase the number of HSC and MSC before they begin to differentiate. These systems tend to use growth hormones and other synthetic materials such as recombinant cytokines in order to accelerate the proliferation of the stem cells. In order to repress the differentiation of these cells chemical additives are often added to the culture. Many believe that the addition of these chemicals may cause genetic instability in the stem cells and other unwanted side effects in the long run.

“Another key advantage PLX-1 offers over these systems is that our method is much quicker,” says Aberman. “We do not have to wait several weeks for the stem cells to grow in culture. Once we have obtained the cord blood all we need to do is add the mesenchymal stem cells and within 48 hours the patient can be successfully engrafted with healthy blood-producing cells.”

Pluristem is currently completing pre-clinical studies and expects to begin clinical studies in 2007. Aberman is optimistic that Pluristem will be able to prove efficacy as well as safety early on in the clinical study process. In doing so he believes that Pluristem can reach the market ahead of or around the same time as competitors.

Aberman believes that the safety features built into Pluristem’s all-natural technology will prevent safety problems of this kind and give Pluristem an edge over competitors. An experienced entrepreneur who joined Pluristem at the beginning of the year, Aberman believes that the company also offers investors a competitive financial edge.

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