Placental-derived and expanded mesenchymal stromal cells (PLX-I) to enhance the engraftment of hematopoietic stem cells derived from umbilical cord blood

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For the past 40 years, bone marrow transplantation (BMT) has become standard therapy to re-establish marrow function in patients with damaged or defective bone marrow. A human leukocyte antigen-matched sibling is the donor of choice for patients needing transplantation of allogeneic hematopoietic stem cells (HSCs). As most patients do not have an acceptable matched, related donor, the National Marrow Donor Program has been established to match volunteer bone marrow donors with potential recipients who require BMT. Although transplantation of HSCs from an unrelated donor can be an effective therapy for a variety of malignant and non-malignant diseases, it remains complicated because of treatment-related morbidity and mortality, which has led to the investigation of alternative sources of HSCs such as umbilical cord blood (UCB). This review highlights the advantages and disadvantages of UCB and recent developments that address its disadvantages. This includes the use of a placenta-expanded mesenchymal stromal cell product (PLX-I) being developed by Pluristem Therapeutics, Inc. and our opinion about the potential of this product.

Keywords: bone marrow transplant, hematopoietic stem cell, PLX-I, umbilical cord blood


1. Introduction

Bone marrow transplantation (BMT) or the intravenous infusion of hematopoietic progenitor cells to re-establish marrow function in patients with damaged or defective bone marrow has been a standard of care for the past 40 years [1]. When available, a human leukocyte antigen (HLA)-matched sibling is always the donor of choice for patients needing transplantation of allogeneic hematopoietic stem cells (HSCs). However, only ~30% of candidates eligible for HSC transplantation will have such a donor available. Because most patients do not have an acceptable matched, related donor, the National Marrow Donor Program has been established to match volunteer bone marrow donors with potential recipients who require BMT. The registry is currently composed primarily of Caucasians of Western European descent, making it extremely difficult to find potential donors for ethnic minorities [2]. It has been estimated that ~150,000 people require BMT annually, whereas only 45,000 – 60,000 patients receive them [3]. Although transplantation of HSCs from an unrelated donor can be an effective therapy for a variety of malignant and non-malignant diseases, it remains complicated because of treatment-related morbidity and mortality owing to regimen-related toxicity, infection, bleeding, engraftment failure and acute and chronic graft-versus-host...
disease (GVHD) [4]. This has led to the investigation of alternative sources of HSCs.

This review highlights the role of umbilical cord blood (UCB) as a source of HSCs, the advantages and disadvantages of this source and recent developments that address these disadvantages. One development that is highlighted is the use of a placenta-expanded mesenchymal stromal cell product (PLX-I) being developed by Pluristem Therapeutics, Inc., to enhance the engraftment of HSCs derived from UCB and our opinion relating to the potential of this product.

2. Umbilical cord blood as a source of hematopoietic stem cells

In the early 1900s, UCB was found to be a rich source of pluripotent stem cells that could be used in place of bone marrow in transplantation [5]. UCB has subsequently emerged as a feasible alternative source of hematopoietic progenitors for allogeneic stem cell transplantation, primarily in patients who lack HLA-matched marrow donors. Since the first case of a successful UCB transplantation in a child with Fanconi’s anemia was reported in 1989 [6], there have been thousands of UCB transplants for a variety of malignant and non-malignant diseases. Subsequently, several advantages (Box 1) and disadvantages (Box 2) have been recognized for the application of UCB as a source of HSCs for patients requiring allogeneic transplantation [7].

The major limitation of the use of UCB for HSC transplant is the number of cells needed. Typically, 100 – 120 cc of cord blood can be obtained from the umbilical cord at the time of delivery. However, the number of HSCs needed for transplantation depends on the recipient’s size, and it is unclear if enough number of cells can be obtained from cord blood for transplantation in an adult patient. Consequently, the rate of donor hematopoietic reconstitution is lower and the time to engraftment is delayed using UCB: 30 – 40 days for neutrophils and more for platelets compared with bone marrow grafts, which average 15 – 20 days for neutrophils and platelets. Therefore, most of the UCB transplants have been performed in children and adolescents [8].

Various strategies have been evaluated for their ability to overcome UCB cell dose limitations and to reduce the time to engraftment. These strategies include the simultaneous transfusion of two UCB units from different donors [9], the

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**Box 1. Advantages of UCB as HSCs for allogeneic transplantation.**

UCB is an abundantly available source of stem cells that can be harvested at no risk to the mother or infant

Ethnic balance in a cord blood repository can be maintained and controlled through the collection of UCB from birth centers representing targeted minority populations

There is a low risk of viral contamination of UCB including cytomegalovirus and Epstein–Barr virus

UCB, cryopreserved and banked, is available on demand and can eliminate delays and uncertainties that now complicate marrow collection from unrelated donors

The ‘naive’ nature of UCB lymphocytes permits the use of HLA-mismatched grafts without a higher risk of severe GVHD relative to BMT from a fully matched unrelated donor [47]

There is an undistorted accumulation of HLA genotypes acquired in a UCB bank because stored UCB suffers no attrition except by clinical use, unlike volunteer unrelated adult donor registries in which donors are lost owing to advancing age, new medical conditions or geographic relocation

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**Box 2. Disadvantages of UCB as HSCs for allogeneic transplantation.**

The limited number of HSCs as well as their progeny contained in collected UCB contributes to higher rates of graft failure and a delayed time to engraftment compared with BMT

The limited number of hematopoietic progenitor cells contained in collected UCB also contributes to its restricted use in adult recipients

The future development of potential abnormalities of the newborn donor’s HSCs into adult life and their effects on the recipient is unknown at the time of transplant

The infeasibility to collect extra donor HSCs for patients experiencing graft failure or donor lymphocytes for recipients who relapse after initial UCB allografting

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BMT: Bone marrow transplantation; GVHD: Graft-versus-host disease; HLA: Human leukocyte antigen; HSCs: Hematopoietic stem cells; UCB: Umbilical cord blood.
in vivo stimulation of UCB stem cells using growth factors or agents that upregulate the expression of intercellular adhesion molecules (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [10], and the in vivo and ex vivo expansion of cord blood stem cells using a variety of techniques [11-15]. One such in vivo technique that is being developed by Pluristem Therapeutics, Inc., is the co-transplantation of allogeneic mesenchymal stromal cells (MSCs) that are derived from the human placenta with UCB.

3. Mesenchymal stromal cells

Adult stem cells that can differentiate into non-hematopoietic tissue have been identified by Friedenstein >35 years ago when he isolated a portion of the bone marrow that attached to tissue culture surfaces and was able to differentiate into osteoblasts, adipocytes, and chondrocytes [16]. These cells were later termed marrow stromal cells because they seemed to originate from the supporting structures of the bone marrow and served as feeder layers for HSC cultures. Commonly termed mesenchymal stromal cells, many studies on animals and humans have demonstrated a significant ‘plasticity’ to these cells. This ‘plasticity’ refers to the ability of stem cells to cross lineage barriers and adopt the expression profiles and functional phenotypes of cells from other tissues [17-19].

While the standard test to confirm the multipotency of MSCs is differentiation of the cells into osteoblasts, adipocytes, and chondrocytes, it is clear that under the influence of appropriate signals these MSCs are found to be able to evolve into cells with ectodermal, endodermal and mesodermal characteristics. It may be that MSCs in adult tissues are reservoirs of reparative cells, ready to mobilize and differentiate in response to wound signals or disease conditions.

3.1 Immunogenicity and immunomodulating properties of mesenchymal stromal cells

Although researchers have advised continued investigation [20], an emerging body of data indicates that MSCs escape recognition of alloreactive cells and are considered to have immunomodulatory properties [21-23]. Having low immunogenicity, MSCs are potentially not rejected by the patient’s immune system, and therefore are considered not requiring HLA matching.

MSCs generally express only HLA class I. Despite a few studies that have demonstrated that MSCs can be induced by IFN-γ to upregulate to HLA class II, neither the human MSCs that expressed HLA class I only nor the MSCs that were exposed to IFN-γ and expressed both HLA class I and II showed immunogenic potential. Furthermore, both cell types could inhibit T-cell immune responses, and the upregulation of HLA class II by IFN-γ did not elicit a proliferative response of T cells [19,24].

Bone marrow-derived MSCs have been shown both in vivo [25,26] and in vitro [27,28] to suppress T-cell activation. Additionally, MSCs have been shown to suppress the proliferation of activated T cells induced by allo-antigens in the mixed lymphocyte reaction (MLR) [23] and induced by mitogens such as phytohemagglutinin [29] or concanavalin A [19] as well as the activation of T cells by CD3 and CD28 antibody stimulation [30]. Several studies have shown similar effects when using MSCs that are autologous or allogeneic to the responder cells, indicating a genetically unrestricted suppression [31].

3.2 How mesenchymal stromal cells exert their beneficial effects

Although the differentiation potential of MSCs has been repeatedly demonstrated [32], an interesting observation is that these cells frequently provide functional improvements without showing evidence that the cells neither engrafted nor differentiated. This suggests that MSCs help repair tissues in ways other than through their stem cell characteristics. Although the exact mechanisms of action of how MSCs exert their benefits on damaged tissue remain a mystery, there are several hypotheses proposed. For example, it has been shown that cells are able to secrete a large number of cytokines and chemokines in culture [33]. Additionally, the pattern of secreted cytokines and chemokines changed after the cells engrafted into new tissue. Therefore, it has been postulated that one mechanism of action is that MSCs stimulate the regeneration of damaged tissue.

Additionally, as noted, bone marrow-derived MSCs have been found to suppress the MLR in culture and were subsequently proven to improve the engraftment of bone marrow and lessen GVHD in patients [34]. Therefore, it has been postulated that another potential mechanism of action for the reparative qualities of these cells is their ability to suppress immune reactions.

3.2.1 The effect of mesenchymal stromal cells on hematopoiesis

The multipotential ability of MSCs, their easy isolation and culture as well as their high ex vivo expansive potential make these cells an attractive therapeutic tool [35,36]. In their normal role in the bone marrow microenvironment, it is believed MSCs create the conditions that enable hematopoiesis. Initially, one of the proposed mechanisms for the enhancement of engraftment of HSCs by MSCs was the homing of donor MSCs to the recipient bone marrow. However, current evidence indicates that marrow stromal cells are host-derived. Thus, it is thought that MSCs enhance engraftment and support hematopoiesis by mechanisms that may not require homing of MSCs to the bone marrow and may be mediated by the release of cytokines that promote either the homing or proliferation of HSCs [32]. MSCs provide biological support for HSCs by constitutively

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secretion of cytokines important for HSC differentiation, including IL-1, IL-6, IL-7, IL-8, IL-11, IL-12, IL-14, IL-15, IL-27, leukemia inhibitory factor, Flt-3 ligand, stem cell factor (SCF), G-CSF and GM-CSF [27].

Another important characteristic of MSCs as it relates to hematopoiesis is cell-to-cell contact. MSCs express surface molecules that can interact with cells of the hematopoietic lineage, including ICAM-1 (CD54), ICAM-2 (CD102), VCAM-1 (CD106), lymphocyte function-associated antigen 3 (CD58), activated leukocyte cellular adhesion molecule (CD166), hyaluronic receptor (CD44) and integrins such as very late activation antigen (CD49) [32].

In addition to providing critical cell-to-cell interactions and producing growth factors for hematopoiesis, MSCs may attract infused HSCs to the marrow. It is well known that stroma-derived factor (SDF)-1 has significant importance on the homing of HSCs to their niche in the bone marrow. It was demonstrated that SDF-1 affects the recruitment of CD34+ cells to the marrow in a NOD/SCID (non-obese diabetic/severe combined immunodeficient) model of human hematopoiesis [27]. Thus, MSCs have a role in homing by both inducing the expression of SDF-1 through secretion of SCF and directly by secretion of SDF-1.

MSCs are stable adhesive cells that can be expanded in vitro without loss of phenotype and without showing signs of karyotypic changes [27,32]. Primary mesenchymal cells derived from fetal or adult sources promote the engraftment of UCB-derived CD34+ cells to a similar degree as culture-expanded MSCs, indicating that the biological properties of primary mesenchymal cells are preserved during expansion, as is the potential safety profile of culture-expanded cells for therapeutic application [37].

### 3.3 Mesenchymal stromal cells derived from the placenta

Although most of the work performed on MSCs has been derived from autologous bone marrow, Pluristem has focused on using MSCs derived from the placenta and used allogeneically.

MSCs can be isolated from a full-term human placenta [38-40]. Placental-derived mesenchymal cells exhibit many markers common to MSCs isolated from other tissues, including CD105 and CD73, CD90 and CD29, and lack the expression of hematopoietic, endothelial and trophoblastic-specific cell markers. Adipogenic, osteogenic, and neurogenic differentiation have been achieved after culturing placental-derived MSCs under the appropriate conditions [41]. Thus, the placenta provides an ethically uncontroversial and easily accessible source of MSCs for future experimental and clinical applications [35].

MSCs isolated from placenta and cultured in vitro have also been demonstrated to suppress the proliferation of T cells triggered by allogeneic peripheral blood and UCB-derived T lymphocytes in MLR [25]. This effect was dose-dependent and still occurred when MSCs were derived from a third party. This shows that placental-derived MSCs are similar to bone marrow-derived MSCs. As a result, they have potential application in allograft transplantation and can be transplanted with HSCs from UCB to reduce the potential GVHD in recipients [25,35].

### 4. Pluristem Therapeutics, Inc.

Pluristem Therapeutics, Inc., based in Haifa, Israel, is a regenerative, bio-therapeutics company dedicated to the commercialization of non-personalized (allogeneic) cell therapy products. The company is expanding non-controversial placental-derived MSCs through a proprietary 3D process, termed PluriX™. Pluristem will be conducting Phase I trials in the US with its placental-expanded MSCs (termed PLX-I cells), which will address the global shortfall of matched tissue BMT by improving the engraftment of HSCs contained in UCB.

#### 4.1 Pluristem’s expansion of mesenchymal stromal cells

Traditionally, MSCs have been plated and enriched using standard cell culture techniques. Cells are usually cultured in basal medium in the presence of fetal bovine serum with the addition of growth factor supplements such as FGF-2, leukemia inhibitory factor and EGF.

Pluristem’s proprietary position in the expansion of placental-derived MSCs surrounds the growth of these cells in a 3D bioreactor (on a non-woven fibrous matrix), termed PluriX™. In the PluriX™ system, MSCs home onto the polystyrene rungs of the matrix and expand to as much as 6.5 × 10^6 cells/g of matrix without the use of growth factors or other supplements. Pluristem has termed these placental-derived, 3D-expanded MSCs as placental expanded (PLX) cells (Figure 1).

The major steps involved in the production of PLX cells include i) receiving, recovery and processing of the MSCs from the disease-free placenta of a full-term delivery; ii) certifying the placenta for use as 2D-cell-stock; iii) inoculating the 2D-cell-stock into the PluriX™ 3D bioreactor; and iv) harvesting, filing and freezing of the PLX cells in liquid nitrogen.

#### 4.2 The cytological, immunological and immunomodulating characteristics of Pluristem’s PLX cells

Scientists at Pluristem’s research center in Haifa, Israel, have demonstrated that PLX cells show an almost identical surface profile related to the expression of mesenchymal markers and the absence of hematopoietic, dendritic and endothelial markers. Typical MSC surface markers, such as CD105, CD73, CD90 and CD29, are highly expressed by PLX cells. Markers for hematopoietic (CD45, CD34), endothelial (CD31) or dendritic cells (costimulatory molecules CD80, CD86, CD83) and trophoblastic-specific cell markers were also demonstrated to be significantly reduced compared to bone-marrow-derived MSCs.
CD86) could only be located at extremely low levels in some cells. The surface markers of these adherent PLX cells, compared with bone marrow-derived MSCs, strongly indicate a MSC-like phenotype.

Additionally, it has been shown by both Pluristem as well as independent researchers that PLX cells may not only be immune-privileged but also immunosuppressive. Figure 2 outlines an MLR reaction using peripheral blood samples from two separate donors (PB-A and PB-B) and PLX cells (PLX-I) [42]. The addition of PLX-I to PB-A evoked no response and suggests PLX cells are immune-privileged whereas the addition of PB-A to PB-B evoked a considerable stimulation of lymphocytes. Thereafter, there was a dose-dependent reduction in lymphocyte stimulation with the addition of PLX cells suggesting that PLX cells are immunosuppressive.

The way in which PLX cells suppress T-cell activation and modulate the immune response has not been completely resolved. However, several mechanisms have been proposed and PLX cells have been shown to have a variety of significant effects. Immune suppression seems to be mediated by soluble factors produced by PLX cells. It is unlikely that the factors are constitutively secreted by the cells because cell-free PLX culture supernatants fail to suppress alloreactivity, whereas supernatants from PLX/lymphocyte cocultures are suppressive.

Additional data suggest that PLX cells possess immunomodulatory characteristics. For example, when compared with MSCs derived from the bone marrow, PLX cells have been demonstrated to prevent the proliferation of pro-inflammatory cells, downregulate pro-inflammatory cytokines and enhance the production of anti-inflammatory cytokines (Figure 3).

Figure 4 demonstrates this phenomenon. Human-derived peripheral blood mononuclear cells were stimulated with concanavalin A in the presence of PLX cells for 96 h. The supernatants were collected and subjected to cytokines analysis using ELISA methods for IFN-γ. The PLX cells reduced the secretion of IFN-γ in a dose-dependent manner. Similar results were seen for TNF-α [43].

The fact that PLX cells secrete these cytokines in similar or higher amounts than human bone marrow suggests that
Enhancement of the engraftment of hematopoietic stem cells by PLX-1 cells

Figure 3. The immunomodulation properties of Pluristem’s PLX cells [48].
B: B cell; CTL: Cytotoxic T lymphocyte; DC: Dendritic cell; MSC: Mesenchymal stem cell; NK: Natural killer; T: T cell.

Figure 4. The influence of Pluristem’s PLX cells on the secretion of IFN-γ in ConA-stimulated mononuclear cells.
ConA: Concanavalin A; PB: Peripheral blood.
PLX cells may play a role in the hematopoietic recovery in the patient and thus may fulfill its purpose to shorten the time to engraftment.

PLX cells seem to escape the immune system, and this makes them potentially useful for various transplantation purposes. PLX cells express intermediate levels of HLA MHC class I molecules and do not express HLA class II antigens on the cell surface.

Pluristem believes important immunomodulation differences such as those noted above could potentially allow the PLX cell to play a major role in the prevention or treatment of cellular transplantation reactions such as GVHD. Additionally, the company believes the uniqueness of the PLX cell could be the basis for a cell proprietary only to Pluristem.

When considering the use of Pluristem’s PLX cells for use in HSC engraftment, in in vitro studies Pluristem has shown that PLX cells secrete SCF at levels similar to and IL-6 at levels higher than human bone marrow. These cytokines are known to be secreted in the bone marrow as hematopoietic support cytokines and to have a role in hematopoietic differentiation (Table 1) [32].

When PLX cells were present in mixed lymphocyte cultures or to lymphocytes that were stimulated by mitogens, cell proliferation was modulated in a dose-dependent manner. The suppression of allogeneic T-cell proliferation, as well as the T-cell response to mitogens, was clearly observed by the addition of PLX cells suggesting that these cells are immunosuppressive.

4.2.1 The therapeutic potential of PLX-I, an MSC-derived product

PLX-I is Pluristem’s name for their PLX product intended to improve the effectiveness of engraftment and shorten recovery times during the transplantation of HSCs contained within UCB. Pluristem’s goal is that, after production, PLX-I is stored ‘ready to use’ and the patient does not have to wait several weeks for stem cells to grow in culture. Once matched cord blood is found, PLX-I is intended to be used immediately on arrival to the hospital with PLX-I being administered intravenously before the UCB injection to improve engraftment.

4.2.2 Pluristem’s preclinical results with PLX-I

In a study conducted by researchers at Pluristem [44], the enhancement of engraftment of HSCs using PLX-I was tested in both sublethally irradiated (350 rad) and chemotherapy (50 mg/kg busulfan) treated 7 – 8-week old NOD/SCID mice. In these animals 50 – 100 × 10^3 human UCB-derived CD34+ cells were injected into the tail vein along with either 0.5 × 10^6 or 1.0 × 10^6 PLX-I cells. Following 5 – 6 weeks, bone marrow FACS analysis showed a significant increase in the % hCD45+ rate in mice transplanted with PLX-I cells compared with mice transplanted with CD34+ cells alone: 13.6 versus 31.7, p = 0.01, (n = 6) in the irradiation setting and 28.8 versus 6.3, p < 0.05 (n = 7) in the chemotherapy setting (Figure 5). These investigators have indicated that these preclinical results demonstrate the potential of human placental-derived MSCs, grown as a 3D culture (PLX-I), to promote human UCB CD34+ cell engraftment in bone marrow and that co-transplantation of PLX-I may be considered for improving the delayed engraftment using UCB as the source of HSCs.

4.2.3 Pluristem’s planned Phase I clinical trial with PLX-I

Pluristem is planning a Phase I dose escalation trial of PLX-I as an adjunct to UCB transplantation. The long-range goal is to co-transplant an effective dose of PLX-I with UCB to hasten the time to donor cell engraftment and hematopoietic reconstitution of the HSCs contained in UCB. This Phase I, open-label, dose-escalating study will involve patients with a hematological malignancy who are unable to undergo a traditional BMT owing to the lack of suitable donor and who would be eligible for UCB transplantation.

4.2.3.1 Formulation of PLX-I for the trial

Each unit of PLX-I will contain 40 × 10^6 PLX-I cells in 4 ml of a 3D-freezing mixture. The 3D-freezing mixture contains 25% (v/v) human albumin, 10% DMSO and 65% physiological solution. Each unit will be stored in gas-phase liquid nitrogen in 5 ml freezing tubes and the product will be shipped at a temperature of -180°C in liquid nitrogen.

4.2.3.2 Dosing of PLX-I for the trial

This first study is designed according to a traditional Phase I protocol with two dose levels, 2 × 10^6 PLX-I cells/kg recipient body weight and 10 × 10^6 PLX-I cells/kg recipient body weight. A cohort of three patients will be enrolled at each dose level, with an extra cohort of three patients at the final dose so that the dose determined to be safe will have been administered to six patients. In the event of an NCI Common Toxicity Criteria grade 3/4 adverse event, more patients will be accrued. The cells will be infused intravenously 4 h before the UCB graft in an effort to unequivocally attribute any observed toxicity to the PLX-I cells.

4.2.4 Objectives of the trial

The primary objective of this Phase I trial is to determine the safety of PLX-I co-transplantation with an UCB graft in...
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patients undergoing UCB transplantation. The secondary objective is to gather data to determine if PLX improves engraftment parameters after UCB, specifically the time to neutrophil and platelet reconstitution.

5. Expert opinion

Although there has been no previous human experience with PLX-I or any allogeneic MSC derived from the placenta, there have been clinical trials until now using allogeneic MSCs derived from the bone marrow to promote the engraftment of HSCs from UCB.

In 2005, Lazarus et al. [45] reported in an open-labeled multi-center study the co-administration of culture-expanded MSCs with HLA-identical sibling-matched HSCs in patients with hematological malignancies. Patients received either bone marrow or peripheral blood as their HSC source. These patients who received a co-infusion of allogeneic MSCs along with allogeneic bone marrow or peripheral blood tolerated the procedure well without infusion-related adverse events. The median times to neutrophil and platelet engraftment were 14 days (range, 11 – 26 days) and 20 days (range, 15 – 36 days), respectively [45].

In 2007, Le Blanc et al. [46] reported on seven patients who underwent treatment with allogeneic MSCs, together with allogeneic HSC transplantation. The HSC donors were HLA-identical siblings in three cases, HLA-A, -B and DR-β1 identical matched unrelated donors in two, one major HLA-antigen mismatched unrelated donor in one and an unrelated one HLA-antigen mismatched cord blood in one. Neutrophil counts > 0.5 × 10⁹/l was reached at a median of 12 days and platelet counts > 30 × 10⁹/l was achieved at a median of 12 days. The authors conclude that co-transplantation of MSCs resulted in the rapid engraftment of absolute neutrophil counts and platelets and 100% donor chimerism, even in three patients re-grafted for graft failure/rejection.

There was no acute toxicity and no sign of ectopic tissue after transplant [46].

There were two patients in this study whose treatment we believe most closely correlates with the therapy in Pluristem’s PLX-I trial and includes one patient who was a 9-year-old male suffering from severe aplastic anemia. He had a previous graft rejection and his MSC source was a 37-year-old haploidentical female’s bone marrow and his HSC source was the one major HLA-antigen mismatched unrelated donor’s bone marrow mentioned above. The time for his neutrophil counts to exceed > 0.5 × 10⁹/l was 28 days and platelet counts to reach > 30 × 10⁹/l was 20 days. Another patient was a 1-year-old male suffering from severe combined immunodeficiency. His MSC source was a 31-year-old haploidentical male’s bone marrow and his HSC source was the HLA-antigen mismatched cord blood mentioned above. The time for his neutrophil counts to exceed > 0.5 × 10⁹/l was 24 days and platelet counts to reach > 30 × 10⁹/l was 36 days.

We believe these studies demonstrate that using allogeneic MSCs derived from the bone marrow to improve the engraftment of HSCs from bone marrow or peripheral blood is safe. We also believe that allogeneic MSCs obtained from the placenta for this indication will also prove to be safe. Additionally, PLX-I infusions may have a dramatically positive therapeutic impact on hematopoiesis and possibly diminish GVHD.

If this is the case, PLX-I may be the first MHC unmatched MSC product obtained from unrelated third party donors that could become an ‘universal donor product’ with these cells readily available in large quantities at a relatively low cost.

Declaration of interest

The authors are employed by Pluristem Therapeutics.
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