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Research

As the full potential for of cord blood is as yet unknown, there is a great deal of research currently being undertaken to discover it capabilities. This chapter summarizes the current state of that research and discusses the potential future applications of cord blood both for research and for the treatment of different diseases and conditions. In addition, because researchers have cord blood unit selection needs that differ from those of transplant physicians, the committee proposes an approach to prioritizing use.

IMPROVING CURRENT TRANSPLANT TECHNOLOGY

As discussed in Chapter 2, cord blood transplantation as a treatment for children with hematological, immunological, metabolic, and neoplastic diseases has been highly successful. The advantage of cord blood transplants is the relatively low rate of graft-versus-host disease (GVHD) compared with the rates of GVHD that occur as a result of bone marrow or peripheral blood transplants. This low rate of GVHD related to cord blood transplantation allows for the use of partially HLA-mismatched cord blood units. However, because of the comparatively low number of hematopoietic progenitor cells (HPCs) in a single cord blood unit, transplantation of cord blood into larger and heavier adult patients presents a unique set of complications. The primary problem for larger patients has been prolonged time to hematopoietic recovery and immune reconstitution related to the low progenitor cell dose per kilogram of patient weight. This delayed recovery is associated with a high rate of treatment-related morbidity and mortality.

Research related to the improved clinical use of cord blood is being conducted in four general areas: (1) enhancement of cord blood engraftment, (2) improvements in immune reconstitution, (3) reduction in the rates of treatment-related mortality, and (4) augmentation of immune recognition of infectious agents and tumors. Further research is needed to better understand how cord blood may be used as a source of effector cells (i.e., performing a specific function in the immune system in response to a stimulus).outside the transplant setting. This includes the development of immune regulatory cells that might be

useful in solid-organ transplant or for the treatment of autoimmune diseases. Cord blood could also be a source of pluripotent stem cells. Research suggests that these pluripotent stem cells, which are capable of differentiation into, for example, hepatocytes and neural progenitor cells, might be present in cord blood.

Research that may improve the effectiveness of cord blood transplantation for the treatment of a variety of conditions is ongoing, including: nonmyeloablative regimens; the use of ex vivo expansion to increase the numbers of HPCs the development of new approaches to the acceleration of immune recovery; the use of multiple units in transplantation; the coinfusion of mesenchymal stem cells (MSC); and facilitation of the upregulation of homing receptors.

Cord Blood Transplantation after Non-myeloablative Therapy

While cord blood as an alternative HPC source has several advantages, including rapid availability and lower risk of GVHD despite HLA-disparity, many older patients, or those with extensive prior therapy or serious co-morbidities, are unable to tolerate conventional myeloablative conditioning. In myeloablative conditioning, the patient's healthy cells are destroyed along with the cancer cells during chemotherapy and total body irradiation. Therefore, reduced intensity or non-myeloablative regimens are being investigated using either related or unrelated volunteer donors. However, given many patients will not have a suitable adult donor, use of unrelated donor cord blood in combination with non-myeloablative conditioning is being investigated in adults to further extend access to allogeneic transplant.

Several studies have been reported thus far. McSweeney et al. (2001) observed engraftment in 2 of 3 evaluable patients receiving fludarabine and total body irradiation 200 cGy. Chao et al. (2002) observed engraftment in 3 of 5 in patients receiving fludarabine cyclophosphamide and antithymocyte globulin. Barker et al. (2003) observed an incidence of sustained donor engraftment in 90 percent (of 51 patients) at a median of 8 days (range 5-32) with complete chimerism¹ in all. Importantly, in a patient population whose median age was 50 years (range 19-60), the incidences of grade II-IV and III-IV acute GVHD were 61 percent and 27 percent, respectively. Despite this risk of acute GVHD, the 6-month treatment related mortality was low at 18 percent. Factors influencing treatment-related mortality at 6 months were age and poor fitness. Notably, patients older than 45 years of age had a treatment-related mortality of 11 percent. Together, the results indicate that cord blood transplantation after a nonmyeloablative therapy can be associated with a high probability of chimerism, indicating that the alloreactive response of cord blood lymphocytes is sufficient for engraftment and a low incidence of treatment-related mortality despite older age.

¹The presence of more than one genetically distinct set of cells in an individual..

Ex Vivo Expansion of Cord Blood Derived Hematopoietic Progenitor Cells

Due to the relatively low volumes of cord blood typically collected, researchers have been interested in developing approaches to increase the volume ex vivo prior to transplant. Ex vivo expansion involves the use of a growth factor to culture a portion of the cord blood unit to increase the numbers of progenitor cells available for transplantation. Cairo and Wagner (1997) have found that 14-day expansion cultures stimulated with interleukin-2 (IL-2) and granulocyte colony-stimulating factor achieved an 80-fold increase in the number of CD34⁺ cells as compared with the increase in the number of CD34⁺ cells achieved with similar bone marrow cultures. The cord blood units are generally divided. One part is cultured, and the remainder is frozen so that the expanded portion of the cell culture can be enriched before transplantation (Cairo and Wagner, 1997; Timeus et al., 2003). The cells for culture are purified and then plated in liquid culture for several days.

There are, however, several challenges with regard to ex vivo expansion of cord blood. Notably:

- there is a time delay in increasing the cell dose based on the number of immature progenitor cells available within the sample (Kogler et al., 1998),,
- cord blood is generally frozen as a single product;; however, clinical trials involve ex vivo expanding a fraction of the unit and then recombining it with the remainder to increase cell dose (McNiece 2004), and
- some of the companies that produce clinical grade reagents for laboratory trials have begun limiting availability to academic centers.

One primary concern is that expansion may induce commitment of and differentiation in HPCs and exhaust their capacity to self renew (Jaroscak et al., 2003). At this point, there has been no late graft failure from ex-vivo expanded units in humans, but the follow-up period post-transplant ranges only from 8-51 months (Kogler et al., 1999; Pecora et al., 2000; Fernandez et al., 2001; Shpall et al., 2002; Jaroscak et al., 2003). Clearly, more research is needed to determine if long-term engraftment is successful and whether expanded units maintain functional hematopoietic repopulating cells. In addition, some argue that the cost and resources required to perform expansion far outweigh the minimal clinical benefit demonstrated to date (McNiece, 2004).

Approaches to Accelerate Immune Recovery

The success of allogeneic HPC transplantation regardless of graft source (including cord blood) is limited in part by slow immune reconstitution and consequent increased risk of opportunistic infection. After the infusion of marrow, peripheral blood, or cord blood, immune recovery first results from the immune cells already present in the graft and subsequently from immune cells derived from the HPC. The pace of immune recov-

ery is dependent upon a number of host and donor factors including: HLA match, age of the recipient, development of GVHD, and duration of and types of immune suppressive therapy employed.

Considerable research to effect more rapid immune recovery includes: pharmacological approaches to induce tolerance, infusion of immune cells that specifically target the more common lethal infectious agents (e.g., CMV, aspergillus), and infusion of T-regulatory cells. These potential solutions are being explored and are not specific to any one graft source (Godfrey et al., 2005).

Multiple Cord Blood Unit Transplantation

Based on outcomes data and risk factor analysis, it is clear that limited cell dose is an important obstacle for recipients of cord blood. One strategy to overcome the limitation of cell dose is infusion of multiple units of partially HLA-matched cord blood from different donors.

Literature review reveals the prior use of multiple cord blood units in the treatment of malignancy as early as the 1970s (Ende and Ende, 1972; Shen et al., 1994; Weinreb et al., 1998; Barker et al., 2001; De Lima et al., 2002). However, only more recently have chimerism assays by molecular techniques been used to determine the contribution of each unit to hematopoiesis after cord blood transplantation. Barker et al. (2001) and de Lima et al (2002) were the first to report “double chimerism” after the infusion of cord blood from two partially HLA matched units. In contrast, Fanning et al. (2003) observed a high rate of graft failure in a study investigating the safety of multi unit cord blood transplantation to achieve a goal of $\geq 5 \times 10^7$ nucleated cells/kg. Seven adults (median age 56 years) with malignancy received cord blood units containing a median of 5.4×10^7 nucleated cells/kg and 2.2×10^5 CD34/kg. While neutrophil recovery occurred at a median of 11 days in 6 patients (with one patient dying on day 55 with mixed chimerism but without neutrophil recovery), 4 failed to have sustained chimerism.

Barker et al. (2001; 2005) reported short-term outcomes in 23 adults (median weight, 73 kg) with high-risk hematological malignancies, using two unrelated cord blood grafts that were 1-2 HLA-mismatched with the patient and each other in 91 percent of the patients. Forty-three percent of the patients received grafts with both units (4/6 matches). Of the 21 evaluable patients, all engrafted at a median of 23 days (ranging from 15 to 41 days), with 24 percent of patients engrafting from both donor units. The remaining patients engrafted from only one donor. In all patients, one unit predominated by day 100. These data demonstrate the safety of double cord blood transplantation in terms of engraftment, thus eliminating the theoretical concern of complete bi-direction immunological rejection. Further, the incidence of grade II-IV was 65 percent and the incidence of III-IV acute GVHD was 17 percent, with 6-month transplant related mortality being 22 percent. With a median follow-up of 10 months (range: 3.5 months-2.5 years), the probability of disease-free survival at 1 year was 57 percent. For those in remission, the disease-free survival rate was 72 percent. The results of these trials indicate that the co-

infusion of two partially HLA matched cord blood units is safe as manifested by high incidence of engraftment.

Importantly alternative strategies using two stem cell sources are also being explored. For example, Fernandez et al. (2001) has demonstrated engraftment of cord blood that has been co-infused with T-cell depleted haploidentical peripheral blood HPC. This approach may represent another important clinical strategy for obtaining an earlier transient wave of long-term neutrophil recovery with hematopoiesis derived from a single cord blood unit.

Coinfusion of Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) are multipotent stem cells capable of self-renewal and differentiation into multiple cell lines (Pittenger et al., 1999; Deans and Moseley, 2000). These cells produce hematopoietic growth factors within the bone marrow environment and as such play an important role in normal hematopoiesis (Dorshkind, 1990; Deans and Moseley, 2000).

In various laboratory studies, MSCs have demonstrated the ability to: promote engraftment by inducing HPC homing receptors (see below); replace stromal cells damaged by the conditioning regimens; produce hematopoietic growth factor; and suppress T-cell responses to allogeneic stimuli (Blair and Thomas, 1997; Deans and Moseley, 2000; Bartholomew et al., 2002; Noort et al., 2002). This has led to a great deal of interest in MSCs among researchers.

In the mouse, cotransplantation of fetal MSC and low doses of CD34⁺ cord blood cells increased engraftment in Severe Combined Immunodeficient (SCID) animals by three- to fourfold (Pecora et al., 2000). Similarly, Kim et al. (2004) have recently successfully infused third-party MSC into mice that were receiving a dual-unit cord blood transplant and achieved a higher level of engraftment.

Thus far, one human study of the use of MSCs with cord blood transplantation has been conducted. In that study, eight pediatric patients with high-risk acute leukemia were coin fused with cord blood from unrelated donors and parental MSCs. There were no serious adverse events, and all patients achieved neutrophil engraftment by day 19 (MacMillan et al., 2002). Although this study demonstrates that MSC can be successfully co-infused with HPC, it is still largely untested and will require more research before any conclusions can be drawn about effectiveness.

Upregulation of Homing Receptors

Research has shown that one of the reasons for delayed hematopoietic reconstitution after HPC transplantation may be the disadvantageous transmigratory behavior of HPCs from cord blood. Short-term treatment with recombinant human stem cell factor (rHuSCF) increased levels of homing-related molecules, thereby increasing their ex vivo

transmigratory potential as well as their in vivo homing potential. Recent studies have revealed that homing receptors and chemoattractants have an important association with the engraftment mechanism after stem cell transplantation. If the numbers of progenitor cells as well as homing potential could be increased by the ex vivo expansion of cryopreserved and unselected cord blood, it would be beneficial for transplantation into adult patients, and it could also improve the engraftment speed (Lee et al., 2004).

Zheng et al. (2003) suggest that optimal engraftment might be expected from ex vivo manipulation of cord blood progenitor cells to “reverse their disadvantageous transmigratory behavior in the clinical setting.”

Another study showed that although expansion of the cord blood CD34⁺ cells may affect other cell properties, it can preserve most of the homing-related characteristics and activities of cord blood (Zhai et al., 2004).

OTHER CLINICAL USES OF CORD BLOOD

In addition to treatment of blood and blood-related diseases, cord blood has the potential to be an effective therapy in certain inherited diseases. The current literature on these uses is summarized in Box 3-1. A comprehensive listing appears in Table 3-1.

Box 3-1.

Examples of Effective Clinical Use of Cord Blood in Treating Inherited Diseases

Fanconi Anemia. First use of cord blood was a sibling with Fanconi Anemia. Several subsequent studies have verified that cord blood is an effective alternative to marrow for the treatment of this disease (Gluckman et al., 1990; Auerbach et al., 1990; Kohli-Kumar et al., 1993; Aker et al., 1999; Guardiola et al., 2003; Guardiola et al., 2004)

Sickle Cell Anemia. Sibling cord blood transplantation has been an effective treatment. Recent research is focused on the use of non-myeloablative preparatory regimens (Brichard et al., 1996; Vermylen and Cornu, 1997; Vermylen et al., 1998; Miniero et al., 1998; Gore et al., 2000; Locatelli et al., 2003; Barker et al., 2005)

Beta Thalassemia. Sibling cord blood, or mixed marrow and cord blood transplantation has been successful. Research on unrelated cord blood transplantation is in the beginning stages (Issaragrisil et al., 1995; Gedikoglu, 2001; Orofino et al., 2003; Goussetis et al., 2000; Orofino et al., 2003; Locatelli et al., 2003; Issaragrisil, 1994; Miniero et al., 1998.)

Hurler Syndrome. Unrelated transplant trials involving twenty-two patients at Duke University have been successful. The stage of the disease at time of transplant has been shown to affect outcome. Larger clinical trials are needed to better understand the full range of cord blood's potential as a treatment (Staba et al., 2004; Muenzer and Fisher, 2004).

Severe Combined Immunodeficiency. Long-term engraftment has been demonstrated in mice. A 2-month-old female was successfully treated with no pre-treatment with a transplant from a fully matched donor (Hogan, et al., 1997).

Osteopetrosis. Bone marrow transplantation is the only fully proven treatment. However, bone reabsorption has been achieved with cord blood transplantation. Due to the strain of conditioning regimens, this treatment is generally only reserved for the most severe cases (Locatelli et al., 1997; NIH, 2000).

Wiskott-Aldrich Syndrome. In a data set involving 33 patients transplanted with units provided by the New York Blood Center, 90 percent engrafted, and 63 percent achieved 5-year survival (New York Blood Center, unpublished)².

TABLE 3-1 Genetic diseases treatable by transplantation of cord blood

Disease
Immune Deficiency
<ul style="list-style-type: none"> • X-linked SCID • X-linked α-γ-globulinemia • Wiskott-Aldrich syndrome • Chédiak-Higashi syndrome • Chronic granulomatous disease • Adenosine deaminase (ADA) deficiency • Purine nucleotide phosphorylase deficiency • Gaucher disease, type 1
Bone Marrow Failures
<ul style="list-style-type: none"> • Osteopetrosis • Thalassemia • Sickle Cell Disease • Fanconi anemia • Dyskeratosis
Metabolic Storage Disorders
<ul style="list-style-type: none"> • Adrenoleukodystrophy • Metachromatic leukodystrophy • Mucopolysaccharidoses <ul style="list-style-type: none"> ○ Hurler • Adrenoleukodystrophy • Metachromatic leukodystrophy • Mucopolysaccharidoses <ul style="list-style-type: none"> ○ Hurler Syndrome ○ Hunter (X-linked) ○ Sanfillippo ○ Morquio • Maroteaux-Lamy • Lesch-Nyhan syndrome (X-linked)

²Personal communication between John Wagner and Cladd Stevens of NYBC (3/13/05).

Umbilical Cord Blood as Effector Cells

More recently, there has been increasing interest in the immune cell populations present in cord blood as a potential source of cells for adaptive immune therapy. For example, cord blood derived NK progenitor and T-cell subpopulations have been isolated and expanded in culture as anti-tumor therapeutic reagents (Miller and McCullar, 2001). Furthermore, CD4⁺ CD25⁺ T cells with profound immunoregulatory properties have been expanded in culture to be used as agents to induce tolerance (Miller and McCullar, 2001). Therefore, it is possible that partially matched or mismatched cord blood units may be important as a source of immune cells and not just as an HPC source for transplant medicine.

UMBILICAL CORD BLOOD IN REGENERATIVE MEDICINE

Although the primary use of cord blood has been to restore hematopoietic function, a number of other potential applications are possible, but these require further research. While there have been limited successes in controlled laboratory settings, it is unlikely that any of these studies will translate into clinical applications in the near future. Rather, they should be considered a guide for future studies using carefully thought-out animal models. Table 3-2 summarizes the present areas of nonclinical research underway with cord blood.

One of the earliest reports that HPC might be capable of generating other tissues was in 1998 (Goodell, 2004). In that study researchers lethally irradiated rats and damaged their skeletal muscles. After the rats received a bone marrow transplant, donor nuclei were found in the skeletal muscles at very low frequencies. Similar studies found that donor-derived cells could also be found in heart, liver, gastrointestinal, and neural tissues. The prevalence of these transdifferentiation events has varied widely, and some researchers feel the event is actually cell fusion rather than transdifferentiation. However, research has continued.

Because early research focused on whole bone marrow, the next step was to refine the marrow to ensure that it was the HPCs and not other cells in the bone marrow that served as the source of the observed donor cells. This has been achieved in several cases and the donor cells have been observed at very low frequencies.

Researchers have observed donor cells in nonhematopoietic tissue among humans who have received sex-mismatched transplants. Most scientists believe, however, that this does not demonstrate transdifferentiation so much as it demonstrates the ability of the donor cells to circulate (Goodell, 2004).

TABLE 3-2 Summary of Current Research

Type of Research	Reference	Status
Cardiac repair	Perry and Roth (2003) Vanelli et al. (2004)	Capillary-like tubes are grown in culture Transplants in animals have led to improved cardiac function
Central nervous system disease	Newman et al. (2004)	Mice with amyotrophic lateral sclerosis improved after transplantation
Spinal cord injury	Saporta et al. (2003)	HPCs engrafted in the area of injury in rats
Stroke	Taguchi et al. (2004) Willing et al. (2003)	Vascular activity in damaged area in mice increased posttransplantation Motor improvement was noted in mice posttransplantation
Brain damage	Jensen et al. (2003)	Hypoxic mice showed improvement posttransplantation
Liver injury	Di Campli et al. (2004)	Potential for transdifferentiation was first noted in humans posttransplantation
Gastrointestinal	Ishikawa et al. (2004)	Minimal transdifferentiation for intestinal tissue was noted

A final open question with regard to cord blood in nonhematopoietic applications is the presence or absence of the more plastic MSCs. MSCs are a rare form of multipotent progenitor cells capable of supporting hematopoiesis and of differentiating into osteogenic, adipogenic, myoblastic, and chondrogenic cell lines. Several investigators (Wexler et al., 2003; Gang et al., 2004; Bieback et al., 2004; Gang et al., 2004) have been able to culture MSCs from human bone marrow, but they have been unable to do so with umbilical cord blood (Bieback et al., 2004). For this reason, these researchers have concluded that given the current level of knowledge, cord blood is unsuitable for cell therapy applications. Similarly, research by Yu et al. (2004) demonstrated the ability to isolate MSCs from cord blood collected after preterm deliveries, but not from blood extracted after full-term pregnancies.

By contrast, Bieback et al. (2004) have been able to isolate MSC-like cells from cord blood. Their success, however, is relatively isolated (63 percent of 59 units), and they were successful only under optimized isolation and culture conditions. It is also worth noting that they were able to generate only osteogenic and chondrogenic progenitor cell lines, but were not able to develop adipogenic-like cells. Gang et al. (2004) were able to grow myogenic precursor cells; however, their ability to do so was limited and growth

seemed to peak at day 3 after the initiation of culture indicating the need for further research.

Some of the more specific research being conducted is summarized in the following sections.

Cardiac Repair

Perry and Roth (2003) have described the present potential for reconstructing human cardiac cells from bone marrow, peripheral blood, and cord blood. They described a study in which cord blood stem cells were treated with vascular endothelial growth factor and basic fibroblast growth factor and noted the formation of capillary-like tubes. Another researcher isolated HPCs from cord blood, cultured them in a pulse duplicator bioreactor on a conduit artery scaffold, and found that the constructs were very similar to those of native tissues (Perry and Roth, 2003).

Vanelli et al. (2004) indicated that the study of cardiac stem cell precursors in human cord blood and bone marrow will lead to a better understanding of the biology of human cardiac cell differentiation, in addition to providing practical applications. They write that studies with animal models have shown that transplantation has led to improved cardiac function. They further note, however, that when transplanting large populations of unsorted marrow or unmanipulated cord blood, researchers should take into account the fact that only a small fraction of such cells will reach the desired organ.

Central Nervous System Disease

Newman et al. (2004) have described some of the current research being conducted using HPCs from cord blood to treat diseases of the central nervous system. A study involving the transplantation of HPCs into mice with amyotrophic lateral sclerosis found that the mice showed improvements in motor function, lost weight, and lived longer than the mice that did not receive the HPCs. The mice in that study received the transplant before the onset of significant motor deficits. They were then analyzed for evidence of donor cells. Some of the donor cells located in the central nervous system were found to express neural cell phenotypes. These are the first data to suggest that donor HPCs are capable of both *in vivo* differentiation and migration to the brain and spinal cord in the absence of injury.

Again, however, much more research is needed before these successes can be considered indicative of what might happen in humans.

Spinal Cord Injury

Saporta et al. (2003) noted the ability of cord blood to target and migrate to areas of damage and engraft therein after intravenous infusion. Building on this knowledge, they examined the ability of cord to target a zone of compression injury in the spinal cord of adult male Sprague-Dawley³ rats.

The researchers compressed the spinal cords of these rats and infused cord blood at either one or five days post injury. By prelabeling the cells, the researchers were able to demonstrate that the cord blood engrafted in the areas of the spinal cord injury. They postulate that the cord blood entered the areas of damage through damaged blood vessels at the site of the injury or through a compromised blood-brain barrier at sites of secondary damage. The harvested cells did not, however, show evidence of differentiation.

In addition to the evidence of engraftment, the rats also showed significant behavioral improvement compared with the behaviors of the rats that had not received the cord blood. The number of cells transplanted, however, was not enough to restore significant motor function.

Recent reports (AFP, 2004) from Korea, however, indicate that cord blood transplantation may have promising applications in humans with spinal cord injury. A 37-year-old woman who had been paralyzed for almost 20 years reportedly regained the ability to walk after she received a cord blood injection directly in the damaged part of the spinal cord. Other researchers (Willenbring et al., 2004) caution against drawing conclusions from this isolated incident, and believe that this research needs to be reliably replicated before it can be regarded as a potential therapy.

Brain Injury

Stroke

In individuals with stroke blockage of the blood vessels leading to certain areas of the brain causes focal ischemia and subsequent degeneration of the tissue (Peterson, 2004). The severity of degeneration depends on the location and the extent of the injury. In most cases, however, recovery from stroke is not a result of the recovery of the tissue but, rather, is a result of the development of new neural pathways in undamaged regions.

Taguchi et al. (2004) modeled stroke in genetically modified SCID mice. Human CD34⁺ cells from cord blood were administered to the mice via the tail vein within 48 hours after an induced stroke. Mice that received the cells displayed new vascular activity within 24 hours of the transplant and had significantly enhanced cerebral blood flow (Taguchi et al., 2004). These mice also displayed significant improvement on behavioral tests compared with behaviors of control mice and mice that received CD34⁻ cells (Taguchi et al., 2004).

³A widely accepted, dependable, and general-purpose strain of rat used as a research model.

Willing et al. (2003) have found that mononuclear cells in cord blood function similarly to MSCs in bone marrow. These investigators also transplanted cord blood into rats with stroke, and although the number of rats was small, they also noted significant improvements in motor skills and behavior compared with those of the rats that did not receive cord blood.

Non-stroke Related Brain Damage

Jensen et al. (2003) researched the potential of cord blood transplantation as a treatment for children who were brain damaged because of hypoxic incidents during birth. They note that the central nervous system, unlike other tissues has a limited regenerative potential. The transplantation of cord blood, they argue, could be a new therapy.

They reproduced the hypoxic injuries in rats and after transplantation noted markedly improved behavior in the rats that received cord blood transplants compared with the behavior of untreated control rats.

Toxic Liver Injury

Di Campli et al. (2004) compared several studies using both animal models and humans and have highlighted the potential of HPCs to transdifferentiate into nonhematopoietic cells. Marrow-derived hepatocytes were first noted in a rat model that showed male cells in female recipients. Those cells not only had the physical characteristics of liver cells, but also demonstrated the appropriate synthetic and metabolic functions.

Di Campli et al. (2004) noted, however, that the time course of the transdifferentiation process has never been fully explored. They also noted that the number of cells present is well below the therapeutic level needed for the effective treatment of some disorders.

Gastrointestinal Disorders

Inflammatory bowel disorders, such as Crohn's disease and ulcerative colitis, often require novel treatments. Ishikawa et al. (2004) analyzed the capacity of human bone marrow- and cord blood-derived progenitor cells to generate gastrointestinal epithelial cells. To do this, they analyzed gastrointestinal specimens from pediatric and juvenile recipients of allogeneic sex-mismatched progenitor cell transplants and looked for evidence of donor-derived cells (Ishikawa et al., 2004). None of the human patients exhibited any chimerism. However, upon closer inspection under an electron microscope, donor-derived cells could be found at frequencies between 0.4 and 1.9 percent.

The researchers then performed similar experiments with mice and T-cell-depleted human bone marrow and cord blood mononuclear cells. They injected these cells into

newborn mice after the mice were subjected to total body irradiation. After determining that the mice exhibited hematological chimerism, the researchers harvested gastrointestinal tissues from the mice. The results of this experiment indicated that xenogenic transplantation can regenerate epithelial cells in intestinal tissue as well as reconstitute lymphocytes.

Gene Therapy

Newman et al. (2004) postulated that HPCs are promising targets for gene therapy. In theory, the progenitor cells within the mononuclear cell population of cord blood can be used as cell-based gene therapy.

DEVELOPING RESEARCH PRIORITIES

The general consensus is that HPCs can be incorporated into nonhematopoietic tissue, but with very low efficiency. Whether cord blood will be the optimal source for the regeneration of nonhematopoietic tissues is unknown (Goodell, 2004). However, strategies are being developed to improve the efficiency of transdifferentiation with the long-term aim of using HPCs in therapies for nonhematopoietic diseases. Further research, including adequate animal studies is clearly needed to better understand the nonhematopoietic potential of cord blood. Furthermore, given the limited availability of cord blood for research purposes it is important that nonclinical units not be discarded or destroyed.

Recommendation 3-1: Federally funded umbilical cord blood banks should have a mechanism by which they can make available for research use units not appropriate for clinical use according to the priority standards developed by the National Cord Blood Policy Board proposed by the committee (see Chapter 7).

The committee suggests that the proposed National Cord Blood Policy Board consider that the following types of research be given priority for nonclinical use of cord blood:

- research funded by the National Institutes of Health
- peer-reviewed research receiving other government funding
- other peer-reviewed research, and
- other unfunded but innovative research proposals.

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