II. Stablishment of the London Cord Blood Bank and Cord Blood Transplantation

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The first successful transplant using umbilical cord blood (UCB) was performed by Gluckman in 1988 on a patient with Fanconi's anaemia using cord blood from an HLA identical sibling. At present, over 2500 patients with conditions such as leukaemia, bone marrow failure and congenital immunodeficiencies have been transplanted using UCB stem cells. This has led to banks of frozen, HLA typed cord blood units in different parts of the world. There are now over 25 cord blood banks (CBB) around the world with more than 100,000 unrelated, voluntarily donated units available for search. A system of FACT accreditation is in place and the international network of cord banks, Netcord, subscribes to the standards and principles of FACT. Netcord has a virtual office that enables searches from cord blood banks in over 9 countries to be done simultaneously and reported to the transplant centre within minutes.

Advantages associated with the use of UCB, as a source of allogeneic stem cells for transplantation include:

a) UCB is abundantly available (>600.000 births/year in the UK) and a discarded source of stem cells which can be easily harvested at relatively low cost and without risk to the mother or infant.
b) Banked UCB units can be microbiologically screened, tested for blood groups, HLA typed, and cryopreserved, available on demand, thus shortening the time it takes to search for a donor.
c) Reduced attrition rate, as is not the case with donors in bone marrow registries.
d) CB stem cells have a greater proliferative potential than those derived from peripheral blood or bone marrow.
e) CB carries a reduced risk of infectious agents such as CMV in the donor.
f) HLA typed units come from a variety of ethnic groups thus expanding the genetic composition of the registry (bank).
g) Cord blood transplantation has been shown to have reduced incidence and severity of acute GVHD. Although the etiology for this advantageous feature of CB is unknown, it is thought to be related to the distinctive immunological characteristics of umbilical cord blood.

The National Blood Service (NBS) established the London Cord Blood Bank (LCBB) in February 1996, with the aim to bank 10,000 donations from volunteer donors, ensuring a high level of quality control and the best possible mix of donors from different ethnic backgrounds. To date over 5,000 donations have been banked and 59 have been issued for transplantation.

Development of tissue and cord blood banking in the UK has led to the introduction of national regulations. As of April 2001 the Department of Health published a Code of Practice for Tissue and Stem Cell Banks, forming the basis for the accreditation scheme in the UK. The LCBB was the first stem facility to be accredited in the UK.

CB is harvested from the placenta ex utero, by dedicated LCBB staff, currently at 3 hospitals. CB units are processed within 24 hours of harvest, using a method to remove plasma and red cells leaving a standard buffy coat volume with 88% recovery of nucleated cells. The final product is cryopreserved with DMSO for long-term storage in liquid nitrogen. In addition DNA, viable cells and plasma samples are archived for future use.

Informed written consent and medical, behavioural and ethnic histories are obtained from the donor mother. Both the CB unit and the donor mother are screened for anti-CMV, HBsAg, anti-HCV, anti-HIV I/II, anti-HTLV I/II and syphilis. The CB unit is typed for ABO, Rh, Kell and molecular typed for HLA-A, B and DR, assessed for cell content pre and post processing, CD34+ cell counts and viability, and screened for bacterial contamination. On completion of all tests, documentation and information gathering, units are reviewed and registered with the British Bone Marrow Registry and NetCord.

CB units are issued after confirmatory and additional microbiology screening of both the donor mother and CB unit, confirmatory and high resolution HLA typing of the donation and typing of the mother. DNA isolated from an integral sample, attached to the frozen donation, undergoes STR analysis to confirm identity of the unit and a sample is seeded in a clonogenic assay to confirm functional viability of the cells.

Between 1998 and 2002, 59 CB units have been issued to 35 transplant centers in 12 countries. 70% were

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issued for malignant disorders, 36% of the units were from non-caucasian donors and 26% of transplants were fully matched, on low resolution HLA typing. Recipient age ranged from 0.3 to 52 years, with 75% under 16 years old. The median number of nucleated cells transplanted was 4.3 x 10^7/kg with a range of 1.2-14.0 x 10^7/kg. Follow up time for 49 transplants ranged from 7 to 47 months with a median of 20 months. Engraftment has been reported in 77% of 49 patients and an overall survival rate of 46% (n = 49) has been achieved.

The number of CB donations issued is relatively small, but the transplant outcomes compare favourably with results of larger cohorts in published studies. This data demonstrates the ability of the London Cord Blood Bank to provide viable CB units as an effective haemopoietic stem cell source for patients in need of an allogeneic transplant.

Following the observation that cord blood could successfully be used in patients requiring HSC transplantation, and that cord blood transplantation was associated with a reduced incidence and severity of acute GVHD, a number of studies describing the immunological characteristics of cord blood cells have now been published.

It has been demonstrated that the majority of T cells in cord blood express the CD45RA phenotype indicating that these cells are immunologically naive. This is in contrast to their equivalent cell population in adult peripheral blood or bone marrow, which consists mostly of cells with immunological memory as defined by the CD45RO phenotype.

It has also been demonstrated that cord blood contains a higher percentage of lymphoid DCs (DC2) than myeloid DCs, compared with adult peripheral blood. These two DC subsets may have a different role in the regulation of the immune response. The myeloid subset is involved in the development of TH1 responses whereas the lymphoid subset seems to be involved in the induction of TH2 regulatory responses (and possibly involved in the induction of immunological tolerance both in vitro and in vivo).

In spite of these important benefits features of cord blood, there are still limitations to its widespread utilization in the clinical setting. For instance, the numbers of stem cells available in a cord blood unit may be insufficient to restore hematological reconstitution in adult patients; clinical evidence shows that a minimum dose of 3.7 X10^6/Kg of TNC (total nucleated cells, containing the HSC) is required for successful engraftment. It is possible that two or more units of cord blood might be required when the dose of TNC is not sufficient, and Wagner in the USA is using this approach. Also it is not yet clear how the reduced incidence and severity of GVHD may affect the development of the graft versus leukemia (GVL) effect, although preliminary clinical and experimental data indicate that the GVL response following cord blood transplantation, may not be impaired. In addition, it has recently been shown, in an analysis of over 1,200 UCB transplants that the degree of HLA matching is directly proportional to the successful outcome of the transplantation (P. Rubinstein, personal communication).