

Cord blood banking

A. Brand, P. Rebull, C. P. Engelfriet, H. W. Reesink, Y. Beguin, E. Baudoux, G. Kögler, M. Ebrahimi, G. Grazzini, A. Nanni Costa, A. Bosi, N. Sacchi, L. Lombardini, S. Pupella, L. Lecchi, E. D. Calderón Garcidueñas, J. M. van Beckhoven, H. J. C. de Wit, W. E. Fibbe, E. B. Zhiburt, T. Bart, M. Beksac, C. Navarrete & F. Regan

Since the first successful haematopoietic stem cell transplantation (HSCT) using cord blood from a sibling in 1988 and the establishment of the first public umbilical cord blood bank in New York Blood Center in 1992, umbilical cord blood banks have been instituted in many countries. Funding was received from regular blood banks, health councils, charity funds or commercial investments. The international medical society is indebted to the New York Blood Center for publishing their procedures and EuroCord for fighting a patent on cord blood processing. Although it is unknown how many cord blood samples are currently banked and have been transplanted worldwide, the figures of the international registration of World Marrow Donor Association (WHDA) show an increase of cord blood use, in addition to other sources of unrelated HSCT (Fig. 1).

Cord blood for HSCT is, in addition to national/regional use, exchanged worldwide. Donor counselling, human leucocyte antigen (HLA)-typing, tests for transmittable diseases and product quality control requirements to comply with (inter)national [AABB, Paul-Ehrlich-Institut, NetCord/Foundation for the Accreditation of Cellular Therapy (FACT)] standards are expensive, making storage of cord blood for unrelated allogeneic haematopoietic transplantation currently a loss-making activity, not particularly attractive for private enterprise. In the last years, hopes have been fueled that other stem cells in cord blood may be used for future repair of metabolic or degenerative diseases. Autologous or personal cord blood banking appeals to individual initiatives and private funding; money is desperately needed by allogeneic cord blood banks, and it would be much better if it could

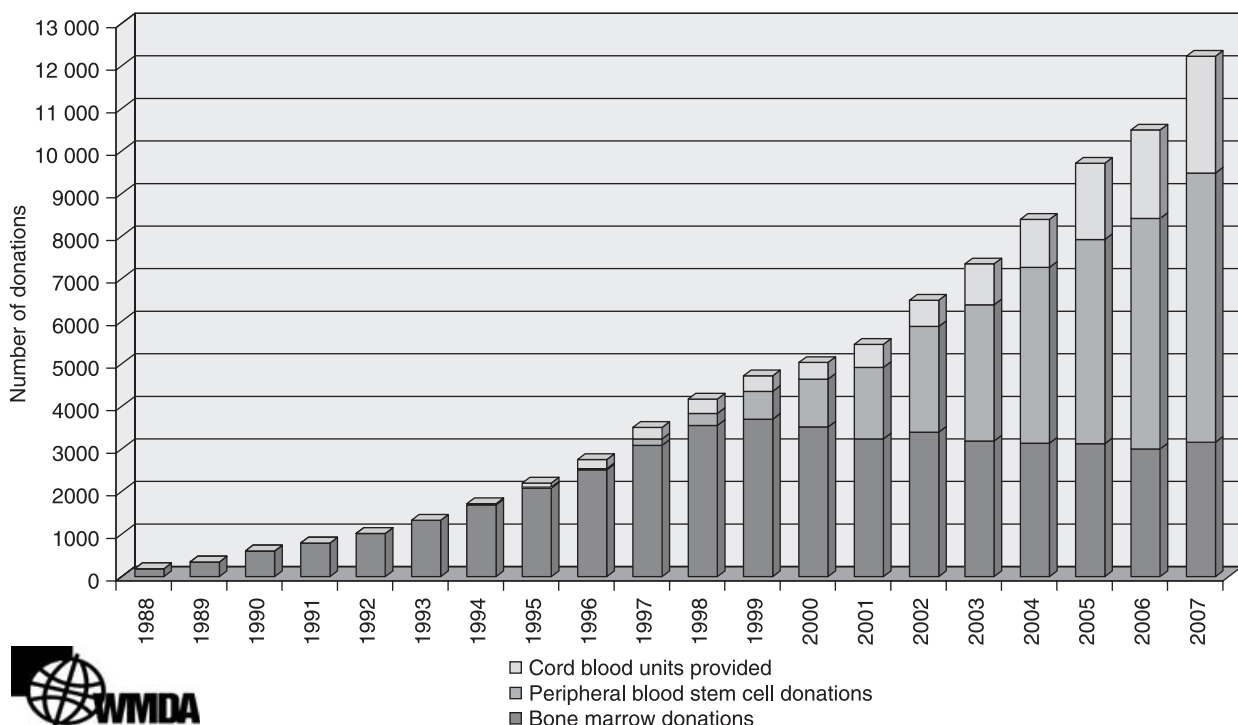


Fig. 1 Stem cell products provided for unrelated patients.

become available to the latter. In spite of the fact that the probability for the use of autologous cord blood is extremely low (estimates range from 1 : 1400 to 1 : 200 000), almost 500 000 autologous cord blood samples (two to three times the number of allogeneic cord blood units) are stored in the USA [1]. In some countries such as India, only private cord blood banks are operating. We aimed to make an inventory of how professional standards of current cord blood banks respond to autologous public cord blood banking. We sent out questionnaires to NetCord-associated banks and national societies for haematology with the following questions:

Question 1. Is/are there cord blood bank(s) in your country in which samples of allogeneic cord blood are stored in non-for-profit institutions? Are they part of a national or international network? Which authority is responsible for these cord blood banks? Do the banks offer opportunity to store allogeneic related cord blood (directed) and/or autologous cord blood samples, and if so, for which indications?

Question 2. Do you agree that some conditions treatable with allogeneic cord blood are already present in the stem cells of the infant, and that therefore such conditions should be treated with allogeneic rather than autologous cord blood? Do you nevertheless feel that the storage of samples of autologous cord blood should be encouraged? If so:

- Should the samples be stored in the not for profit bank where allogeneic blood is stored?
- If you think they should be stored in separate banks, who should be responsible for these banks and how should quality control be assured?
- Do commercial banks to store autologous blood samples already exist in your country?
- Which authority is responsible for these banks?
- How is the quality control of such blood banks assured?
- Are these banks also involved in storing allogeneic (related and/or unrelated) samples? If not, why?

Question 3. Which do you consider appropriate indications for storing directed (related and/or autologous) cord blood samples?

Unfortunately, only 10 responses were received, a disappointing number. However, an interesting international scenario is nevertheless revealed.

In all responding countries, allogeneic (anonymous) cord blood banks are operated by public non-for-profit institutions and the majority are or are in the process of operating in national and international networks, including accreditation. All allogeneic cord blood banks offer, in principle, facilities for the storage of related donations. Generally, the public cord blood banks offer storage of related cord blood samples on request of a transplant physician or a physician who takes care of an affected family member (which often implies that the costs are reimbursed). None of the public cord blood banks currently store autologous cord blood.

In all the participating countries, except the Netherlands and Italy, one or many private autologous cord blood banks are operating. In Italy, private cord blood banking is prohibited, but agents of the international private banks do operate in the Netherlands and Italy with regard to the organization of the collection and exportation of autologous units. In most countries, there is a clear separation between public and private banks with respect to scientific cooperation, quality control, exchange and the responsible authorities. Exceptional situations exist in Turkey and Iran. In Turkey, regulated by law and supervised by the Minister of Health, private autologous cord blood banks are obliged to offer 25% of their stock for allogeneic use, which implies certification and Good Manufacturing Practice (GMP) inspections by health authorities. One such private bank has been certified and five are under evaluation. As there are five public cord blood banks, this may result in an almost equal number of private and public banks complying with the same quality criteria. In Iran, a private autologous cord blood has been running for several years, operated by a scientific institute. The expertise, management and supervisory board of this private cord blood bank will be used as a model for the non-for-profit anonymous allogeneic/dedicated cord blood bank, which aims to join NetCord. In other countries, autologous cord blood banks received local licences and accreditation and none is supervised by an external responsible authority.

None of the responding authors favours encouraging storage of autologous cord blood for haematopoietic reconstitution. The prospect of storing autologous stem cells from other than haematopoietic origin is considered immature and information about what and how to store them is yet not available. In some countries such as Germany, autologous banking is not recommended by the Health Council advisory board (Bundesärztekammer), although nevertheless private autologous cord blood banks do operate. Other European countries refer to the Council of Europe Act 2004/23 that does not preclude autologous cord blood banking, but its requirements discourage personal cord blood banking, because the lack of prospect for future usage must be clearly mentioned to the 'investors'. In some countries such as the Netherlands, the decision to combine autologous with allogeneic cord blood banking is still pending. The public support and the assumption of profit from autologous cord blood banking allowing funding of allogeneic cord blood banking is currently explored. Others point to the delicate conflict of interest that can arise combining private and public interest, and warn that if equal quality levels are applied, autologous cord blood banking will be less profitable.

All of the responding authors favour encouraging directed cord blood donations in particular for siblings with a hereditary disease, for example, haemoglobinopathies. Many suggest that a list of indications for directed cord blood donations should be available and regularly revised. Some

countries require a physician's signature as a guarantee for reimbursement.

In conclusion, currently there is, in most of the responding countries, a clear separation between autologous and allogeneic cord blood banks with respect to funding, quality (control), certification and responsible authorities. All allogeneic banks offer storage of related cord blood, albeit that reimbursement within the healthcare system is often a prerequisite. There is agreement that if scientific research supports autologous cord blood storage, this should be accessible for all patients and incorporated in current public allogeneic banks.

There is much interesting information in the answers from the participants, which cannot be mentioned in this Editorial. The reader is therefore strongly advised to read the individual answers.

Reference

- 1 Ballen KK, Barker JN, Stewart SK, Greene MF, Lane TA: American Society of Blood and Marrow Transplantation: Collection and preservation of cord blood for personal use. *Biol Blood Marrow Transplant* 2008; 14:356–363

A. Brand
Sanquin Southwest Region
Plesmanlaan 1b
2333 BZ
Leiden
the Netherlands
E-mail: a.brand@sanquin.nl

P. Rebulla
Milano Cord Blood Bank
Center of Transfusion Medicine
Cellular Therapy and Cryobiology
Foundation Ospedale Maggiore Policlinico
Mangiagalli e Regina Elena
Via F. Sforza 35
Milan 20122
Italy
E-mail: prebulla@policlinico.mi.it

C. P. Engelfriet
Sanquin Research and
Sanquin Diagnostic Services
Amsterdam
the Netherlands
E-mail: p.engelfriet@sanquin.nl

H. W. Reesink
Sanquin Consulting Services and
Sanquin Diagnostic Services
and Department of Gastroenterology and Hepatology
Academic Medical Center
Amsterdam
the Netherlands
E-mails: h.reesink@sanquin.nl
h.w.reesink@amc.uva.nl

Y. Beguin & E. Baudoux

Question 1

Cord blood stem cells may be donated to a bank for a potential match to any patient who has a disease treatable with allogeneic haematopoietic stem cell therapy. This is a proven and increasingly common practice and has important social value. Whether the allogeneic bank is managed by public or private operators is not critical, provided the activity is run in accordance with the international NetCord/FACT cord blood standards, compliance is documented by NetCord/FACT accreditation and the service of allogeneic cord blood procurement is provided for a reasonable fee.

In Belgium, there are five cord blood banks storing samples of allogeneic cord blood: the Liège Cord Blood Bank at the University of Liège in Liège, the Louvain Cord Blood Bank at the Catholic University of Louvain in Brussels, the Brussels Cord Blood Bank at the Free University of Brussels in Brussels, the Leuven Cord Blood Bank at the Catholic University of Leuven in Leuven, and the Gent Cord Blood Bank at the University of Gent in Gent. They are all part of public university hospitals. The first three banks form a network of cord blood banks with a common inventory under the hub of the Liège Cord Blood Bank; they are affiliated both with the Belgian registry of marrow donors (the Marrow Donor Program – Belgium) and the NetCord international network of cord blood banks. The Leuven cord blood bank is also affiliated with NetCord, while the Gent Cord Blood Bank is only participating in the Marrow Donor Program – Belgium. The cord blood banks must obtain certification from the Ministry of Public Health after expert advice from the Upper Health Council on a yearly basis, with a full inspection once every 3 years. The Liège Cord Blood Bank has obtained NetCord/FACT accreditation in 2005, while the Louvain, Brussels and Leuven Cord Blood Banks are in the process of sending their checklist to FACT in the first part of 2008 in preparation for the NetCord/FACT audit. The banks all offer the opportunity to store directed allogeneic related cord blood when a biological sibling has a disease treatable by allogeneic HSCT. None of these public banks offers storage of autologous cord blood units.

Question 2

Some commercial banks are operating in Belgium, offering families the opportunity to store autologous cord blood samples. They receive cord blood units from Belgium as well as from some foreign countries. As they are not undertaking allogeneic cord blood banking, they are not submitted to the same process of certification by the Ministry of Health. After expert advice from the Consultative Bioethics Council and the Upper Health Council, a Royal Decree was published in 2002, forbidding the collection and storage of autologous cord blood when there is no current indication or an increased

potential (genetic disease in the family ...) for its therapeutic use. The decree was challenged in court by a commercial bank, suspended in 2003 and cancelled in 2005. Since then, there is no law regulating cord blood banking activities in Belgium. The 2004/23/CE European directive published on 31 March 2004 has not yet been translated into Belgian law; several proposals are under discussion in parliament. There is no specific quality control on these banks; none of them has obtained or even applied for NetCord/FACT or equivalent accreditation.

If some day autologous cord blood banking is promoted by society, it should be carried out in public cord blood banks that offer certified guarantees of: absence of conflict of interest; appropriate consent process based on complete, unbiased and balanced information; equal access to all families; and quality assurance system documented by NetCord/FACT accreditation and national certification. However, there is currently no valid argument to promote such activities.

Question 3

Cord blood cells should be collected and preserved in families where a biological sibling has a disease treatable by allogeneic HSCT. This is a medical practice of proven benefit. These diseases should include all those for which allogeneic stem cell transplantation is indicated as currently recognized by international expert organizations, such as the European Blood and Marrow Transplant Group, and possibly all malignant, genetic and severe autoimmune diseases. The stored cord blood unit could then provide the necessary stem cells for allogeneic and/or autologous transplantation with or without genetic manipulation.

There is no appropriate indication for autologous cord blood banking when there is no such disease in the family or a high risk thereof. There are two broad purposes for which collection of autologous cord blood units is advertised, that is, autologous HSCT and tissue regeneration.

1. Autologous HSCT. HSCT is a proven therapy for selected patients with life-threatening malignancies, genetic disorders and autoimmune diseases. Both autologous and allogeneic HSCT can be performed, mostly depending on the disease and age of the patient.

- For malignant disorders, allogeneic HSCT is generally preferable to autologous HSCT, because the donor's immune cells can eliminate the patient's residual malignant cells through the graft-versus-leukaemia effect. There is no such effect after autologous HSCT, rendering it less effective to treat leukaemias and other haematopoietic malignancies.
- Studies have demonstrated the presence of preleukaemic and leukaemic cells in the cord blood of children who later develop leukaemia. Because these preleukaemic cells could cause a leukaemia relapse, the use of autologous cord blood for the treatment of childhood leukaemia would be contraindicated.

- Because HSCs in cord blood carry the same genetic defects as the patients', autologous cord blood transplantation cannot be used to treat any genetic diseases amenable to allogeneic HSCT, such as haemoglobinopathies, immune deficiencies or storage disorders.
- If autologous HSCT is the preferred option for a patient, physicians would favour the collection and transplantation of peripheral blood stem cells (PBSC) over that of cord blood stem cells. Indeed, hematopoietic reconstitution is much faster with PBSC, reducing the duration of hospitalization, the risk of infection and the overall cost of treatment. Cord blood would thus be an option only for the 5–10% of patients who are poor mobilizers.
- Many cord blood units would not be usable, because they contain too few nucleated cells. The Liège Cord Blood Bank discards two-thirds of collected units because of low cell count. Among the remaining top third of units, taking 2×10^7 nucleated cells/kg as a threshold for autologous transplantation, 99% are suitable for children of 20 kg of body weight, but this figure drops to 39% when body weight reaches 60 kg.
- In addition, the cost of collecting autologous cord blood in all neonates and using it in very few of them far exceeds that of collecting and transplanting PBSC when a patient needs them. Belgium counts 10 000 000 inhabitants and approximately 70 000 births per year. The cost of storing one cord blood unit for 10 years is around €3000 (€1500 initial fee + €150 per year). The costs of banking cord blood units from all Belgian newborns over 20 years is thus approximately €4 200 000 000 ($20 \times 70\,000 \times €3000$). The risk of needing an autologous HSCT between 0 and 20 years of age is less than 0.01% (i.e. 100/year for Belgium). Hence, if all autologous HSCT were done with cord blood, the cost per autologous cord blood transplantation would be €2 100 000 (€4 200 000 000/2000), compared to €5000 for PBSC. In a more realistic context where cord blood is used only when PBSCs are not collectable and the number of nucleated cells is adequate for transplantation, the cost would even be 20–40 times this figure. The number per year would be < 2–5/10 million inhabitants.
- 2. Tissue regeneration. Stem cells could be used in the future for tissue repair for degenerative or ischemic diseases of the heart (myocardial infarction), liver, muscle, brain (Alzheimer, Parkinson), endocrine system (diabetes), and other organs. Research investigates the potential of embryonic stem cells, fetal stem cells (including cord blood) and adult stem cells for that purpose.
 - Basic research has demonstrated the existence of pluripotent stem cells in cord blood that can differentiate in a number of ectodermal, mesodermal and endodermal

tissues. However, these cells are present in very low numbers and cannot be retrieved from all cord blood units, in particular from those that have been cryopreserved. It is unknown whether current freezing methods used by cord blood bank would preserve them during long-term storage.

- Experiments using cord blood for tissue regeneration in animals are performed with allogeneic or xenogeneic, not with autologous, cord blood cells. Allogeneic cord blood could become a valuable source of stem cells for this purpose.
- There is no scientific evidence that cord blood contains unique stem cell populations that are not present in adult tissues such as the bone marrow, from which much larger numbers of them can potentially be collected. Furthermore, the cost of collecting autologous cord blood in all neonates and storing it for 60 years [$1500 + (150 \times 60) = \text{€}10\,500$] and using it in few of them (1 : 1000 ?) far exceeds ($\text{€}10\,500\,000$) that of collecting and transplanting marrow stem cells when a patient needs them.
- Clinical protocols of tissue regeneration use essentially autologous bone marrow or mobilized peripheral blood cells, with some preliminary but promising success. No clinical protocol has shown a benefit of autologous cord blood.
- Most of the potential diseases (myocardial infarction, Alzheimer's or Parkinson's diseases, ...) for which regenerative medicine could be an indication occur in patients older than 50 years. What the status and treatment of these diseases will be in 50 years is quite impossible to predict and there is a major risk that all cord blood units collected today will just become obsolete, because other forms of prevention and therapy will have become available. In addition, more stringent quality standards would likely replace current ones and could render old cord blood units not acceptable for clinical use then.

Y. Beguin
Department of Hematology
University of Liège
CHU Sart Tilman
4000 Liège
Belgium
E-mail: yves.beguin@chu.ulg.ac.be

E. Baudoux
Department of Hematology
University of Liège
CHU Sart Tilman
4000 Liège
Belgium
E-mail: e.baudoux@chu.ulg.ac.be

G. Kögler

Question 1

Six allogeneic unrelated cord blood banks are located in Germany that store cord blood in non-profit institutions. The largest cord blood bank with 13 796 (June 2008) stored unrelated cord blood units is the José Carreras Cord Blood Bank in Düsseldorf, the next largest is located in Gauting with 2356 cord blood units (www.netcord.org; June 2008); Mannheim with 1652 cord blood units (www.netcord.org), and banks with smaller inventory are found in Dresden, Freiburg and Erlangen.

The cord blood inventory of the banks in Duesseldorf, Mannheim and Gauting are listed with the international NetCord organization. Due to very strict regulations of the German pharmaceutical production law and the European guidelines, all cellular products must be produced under appropriate GMP conditions in class 100 (EU class A) in an environment in class 1000 (EU class B). Each unrelated cord bank in Germany is required to have legal permission from the local authorities to produce and cryopreserve cord blood products and, in addition, a licence from the Paul-Ehrlich-Institute (Federal Agency for Sera and Vaccines).

The banks that store unrelated cord blood in Germany also provide the opportunity to store directed cord blood in case there is a family indication and upon request of the physician. Autologous cord blood samples are not stored in these banks, based on the statement found in the national guidelines of the official organ of the German Federal Chamber of Physicians (Bundesärztekammer) 'to date there are no medical indications to store cord blood for autologous use' [1].

Question 2

We agree that some conditions treatable with allogeneic cord blood are already present in the stem cells of the infant. The experience of the Duesseldorf Cord Blood Bank shows that three children who donated cord blood developed acute lymphoblastic leukaemia and therefore the cord blood could not be used for transplantation.

At present, there seems to be no need to store cord blood for autologous use. The data available worldwide show that among 2 000 000 stored autologous cord blood units, only 12 were used in a clinical situation [2], in which an unrelated cord blood could also have been used or in a situation in which the treatment/chemotherapy alone was sufficient to cure the child. In a paper from the American Academy of Paediatrics, it was discussed that the likelihood of children to need their own cord blood stem cell is from 1 in 1000 to less than 1 in 200 000 [3].

As stated in the position statement on cord blood for autologous use by the NetCord foundation as of January 2008 [4], the following points should be mandatory for consideration:

If autologous cord blood is stored, the process of collection, processing, testing, banking, selection and release of cord

blood cells should fulfil international standards, such as developed by NetCord/FACT. These standards can be ensured by NetCord/FACT accreditation of the cord blood banks. In addition, the information given to the parents or guardian of an infant must be complete, unbiased and balanced. The informed consent process shall include the purpose of stem cell collection, the possible benefits and risks, and the likelihood that the cells may be used for that particular purpose. Donors shall not be misled about the potential for cells to be used to treat future disease in that donor or to regenerate tissue. Conflicts of interest must be disclosed. The American Academy of Pediatrics made it very clear that the private storage of cord blood as 'biological insurance' should be discouraged [3]. The statements of the World Marrow Donor Association (WMDA) [5] and the European Group of Ethics in Science and New Technologies [6] and many other organizations are of the same opinion.

In Germany, six to eight commercial cord blood banks exist to store autologous cord blood samples. Legal permission from local authorities to produce and cryopreserve autologous cord blood products serves as the basis for quality control. As no or very few autologous units are released for transplantation, data on the ultimate quality control of engraftment and survival are lacking. In addition, the numbers of nucleated cells in the cord blood units stored in these banks are much lower than in allogeneic unrelated units.

New variations on donating Cord Blood

In addition to the public and private donation of cord blood a new type of cord blood donation is now possible in a private company which is, however, legally and morally questionable. This alternative appears to bridge the gap between donating for public use and storing for private use: cord blood can be stored privately when a fee is paid and, if required, it can be released anonymously to a patient. At first glance this variation might look like a sensible solution to the contradiction between "Donating versus Private Storage" since it combines both possibilities. This practice is, however, not compatible with the German standards for a non-related blood stem cell donation. These standards specify that the consent form for donating must include a passage stating that the "expectant mother transfers the collected cord blood to the cord blood bank and waives any claims on it" (7). Moreover, this option is not morally acceptable, since it presents the parents with a dilemma to decide once again. They have already spent a considerable sum of money for the storage of their child's cord blood because they truly believe these cells have great potential use for their child in the future. Now they are forced to decide whether they should give this blood to another person, since, for example, the patient (a child with leukemia) might otherwise die without it. If they decide to release the cord blood to the patient, the money the parents spent is

refunded. This decision, difficult enough as it is concerning the fate of another person, possibly even to decide over life or death, is also dependent on economic factors. Is it really fair to put the parents through such a decision making process? This is not the same situation a bone marrow donor faces who is able to decline at any time prior to donation. By contrast, a bone marrow donation is not without risks to the donor, further the actual bone marrow donation is not performed at the time of registration and the donor can also become sick after registering with the bone marrow registry. The cord blood, on the other hand, is a finished pharmaceutical product ready for transplantation.

Question 3

An appropriate indication for storing directed related cord blood within a family is given, if a sibling already presents an indication (malignant and non-malignant disease) as documented by a physician. However, even in this situation, the parents must be well-informed that statistically there is only a 25% chance that the cord blood will be HLA-matched and therefore the best stem cell source. If the sibling cord blood shows HLA-mismatches, an unrelated cord unit might be preferred for several indications.

Moreover, the storage of autologous cord blood should not be recommended for families, which are at risk for a genetic disease (e.g. severe combined immunodeficiency disease), which could be treated with a cord blood allogeneic stem cell preparation.

During the last 10 years, the public relation activities of the majority of companies storing cord blood for autologous use switched from the treatment of haematological diseases (as clinical data was not sufficiently convincing in contrast to allogeneic cord blood transplantation) to the possible future use in regenerative medicine.

Although there are unique cell populations in cord blood (30–40% of cord blood samples) with high proliferative potential and differentiation potential, several of the populations cannot be recovered from cryopreserved samples or only in very small numbers.

Due to these difficulties to generate rare cells from cryopreserved material, therapeutic application of cord blood cells will probably have to rely on the establishment of fresh cord blood cell banks, with the cells generated from fresh cord blood.

In addition, parents who store cord blood for autologous use must be informed that there are also alternative cell sources, such as autologous bone marrow, which could be used at any time during life.

Although cord blood is a very unique cell source and many papers have been published during the last years on tissue regenerating populations in cord blood, some of the data, unfortunately, are not very consistent and should be reconsidered based on the scientific data and studies.

References

- 1 Bundesärztekammer: Richtlinien zur Transplantation von Stammzellen aus Nabelschnurblut. *Deutsches Ärzteblatt* 1999; 96:B-1010
- 2 Ferrera E, Pasternak J, Bacal N, de Campos Guerra JC, Mitie Watanabe F: Autologous cord blood transplantation. *Bone Marrow Transplant* 1999; 24:1041 (further information on the hompages of: Cryo-Cell, Cord Blood Registry, Viacord, Vita34, Hospital for Sick Children, Vita34)
- 3 Cairo M, Kurtzberg J, Lubin B, Shearer W: Cord blood banking for potential future transplantation. *Pediatrics* 2007; 119:165
- 4 NetCord: *Policy on Banking of Cord Blood for Autologous Use*, 2008; Netcord Newsletter (www.netcord.org)
- 5 World Marrow Donor Association: *Policy Statement for the Utility of Autologous or Family Cord Blood Unit Storage*, May 2006
- 6 European Group on Ethics in Science and New Technologies (EGE): *Opinion no. 19 on Ethical Aspects of Umbilical Cord Blood Banking*, 2004
- 7 ZKRD (Zentrales Knochenmarkspender-Register Deutschland): Deutsche Standards für die nicht verwandte Blutstammzellspende. ZKRD 2007.

G. Kögler
Jose Carreras Cord Blood Bank
Institute for Transplantation Diagnostics and Cell Therapeutics
University of Duesseldorf Medical School
Moorenstrasse 5.
D-40225 Duesseldorf
Germany
E-mail: koegler@itz.uni-duesseldorf.de

M. Ebrahimi

Question 1

Recently, we establish the non-for-profit cord blood bank beside our private Royan Cord Blood Bank.

Unfortunately, not yet, but it is our plan to be a part of a national or an international network as soon as possible.

The Royan Research Institute is responsible for the non-for-profit cord blood bank.

We have planned to develop our non-for-profit bank for both purposes, for treatment of some blood diseases and for stem cell therapy purposes in future.

Question 2

We do agree that such a bank should be non-for-profit, because all of us have the goal to rescue patients, whether they are rich or not. But in some cases when there is a specific disease in the familial history, the probability of the use of autologous cord blood stem cells is high. Maybe in this situation such a family will prefer to use a private cord blood bank.

Usually, a scientific group should be responsible for private cord blood banks and the Ministry of Health (public health and/or specific disease office) should have control of the activity of such banks.

In our country (Iran), we have a private cord blood bank that has been active for 2 years and stores about 3000 units.

The Royan Stem Cell Technology is responsible for our private cord blood bank that is linked to the Royan Institute.

The Scientific Board who are academic staff and all our physicians, technologists follow the JACIE & NetCord/FACT standards. In addition, this centre has been controlled by the public health and specific disease office of Iranian Ministry of Health.

If the donor's parents permit us, we will store samples for allogenic transplantation.

Question 3

In some families with a high incidence of a specific disease in their medical history, directed cord blood donations may be suitable.

M. Ebrahimi
Department of Stem Cells
Royan Institute
P.O. Box 19395-4644
Tehran
Iran
E-mail: marzieh_99@yahoo.com

G. Grazzini, A. Nanni Costa, A. Bosi *et al.*

Question 1

Italian cord blood banks storing cord blood units for allogeneic transplantation are non-for-profit institutions belonging to the public National Health System. In 1996, seven banks coordinated by the Milano Cord Blood Bank voluntarily formed the GRACE (Gruppo per la Raccolta e l'Amplificazione delle Cellule Emopoietiche – Group for the Collection and Expansion of Hemopoietic Cells) network [1]. During 1996–2006, GRACE developed an IT protocol for data sharing into a unique inventory managed by the central hub in Milan, which performed preliminary and extended cord blood unit searches on behalf of the member banks. In 2007, the cord blood searching registry was transferred to the Italian Bone Marrow Donor Registry in Genua, which currently manages the national cord blood registry and performs cord blood unit searches. The data from the Italian cord blood banks are also exported to NetCord and to BMDW [2].

Currently, cord blood banking falls under blood transfusion law no. 219/2005 and derived norms.

A significant reorganization of the Italian cord blood banking network, aimed at including all active banks, was started in 2007 through the combined efforts of the National Transplant Centre and the National Blood Centre in Rome. A national survey on 2007 data was recently completed to update the national cord blood banking activity report. A

total of 19 banks with a global inventory of about 22 000 cord blood units, whose 84% HLA typed, responded to the survey. A detailed report of the 2007 survey will be published soon. At 31 December 2007, 634 cord blood units were released for allogeneic transplantation.

Responsibility for the cord blood banks belongs to the 20 Italian regions, which have the authority to accredit the banks based on a national set of standards. The process of regional accreditation is currently under development. The banks in Milan and Pavia have also been accredited by the FACT.

Directed cord blood units are stored at no charge to the family for consolidated indications of family related haemopoietic transplantation. In agreement with the recommendations of several expert groups and scientific societies, autologous cord blood storage is not offered by the Italian cord blood banks, with the exception of the cord blood bank in Mantua. As a result of the current cord blood banking ordinance, which prohibits private cord blood banking and the request of a monetary fee to the donor, families opting for autologous cord blood storage export the units to foreign banks.

The transplantation procedures performed with cord stem cells complying with the national and international guidelines and standards (GITMO – Italian Cooperative Group for Bone Marrow Transplantation and Jacie).

Question 2

Several reports in the literature document the presence of 'defective' stem cells in the prenatal phase of subjects later diagnosed with conditions requiring bone marrow replacement. Such cases must be treated with an allogeneic rather than an autologous haemopoietic stem cell source in order to prevent recurrences and to exploit the transplant versus cancer effect. For this scientific motivation and for the high possibility of meeting again one's cord blood stem cells still banked ($\geq 90\%$) in case of hypothetical therapeutic need, the autologous storage should not be encouraged.

Although in principle it is largely understandable why a significant number of families are attracted by the option of autologous cord blood storage through aggressive communication media campaigns, we share the views of experts who do not recommend this practice, for the following reasons: (i) there are no proven therapeutic protocols; (ii) costs are substantial; (iii) post-storage cell traceability and quality after several decades is not known; (iv) autologous storage may reduce cord blood availability for allogeneic transplants of proven effectiveness; (v) probability of use is exceedingly low; (vi) biological materials including blood and cord blood should be considered as a common good and not as a commodity. In addition, it should be explained to families that haemopoietic progenitors potentially amenable to the same innovative tissue reparative treatments that will hopefully be

developed in the future for cord blood are cultured and nurtured in optimal conditions in the bone marrow throughout our entire lifetime at zero cost for both the subject and the community.

Question 3

Through the combined effort of several experts of the GITMO, the Associazione Italiana Ematologia Oncologia Pediatrica (Italian Society of Pediatric Hematology Oncology) and the European Blood and Marrow Transplant Group [3], Italian cord blood banks may refer to a recently defined detailed list of approved conditions for directed cord blood storage, which belong to the following main categories: leukaemia and lymphoma, myelodysplastic and myeloproliferative syndromes, plasma cell disorders, severe aplastic anaemia and bone marrow failure syndromes, haemoglobinopathies, histiocytosis, congenital immune disorders, inherited metabolic diseases, osteogenesis imperfecta and a few others. In addition to approved indications, physicians requesting directed cord blood storage must document the clinical appropriateness of the planned transplantation procedure. Directed cord blood storage for families at high risk of genetically transmissible conditions treatable with haemopoietic stem cell transplantation must be approved by a geneticist.

References

- 1 Lazzari L, Corsini C, Curioni C, Lecchi L, Scalapogna M, Rebulli P, Sirchia G: The Milan Cord Blood Bank and the Italian Cord Blood Network. *J Hematother* 1996; 5:117–122
 - 2 Hakenberg P, Köglér G, Wernet P: NETCORD: a cord blood allocation network. *Bone Marrow Transplant* 1998; 22 (Suppl. 1):S17–18
 - 3 Ljungman P, Urbano-Ispizua A, Cavazzana-Calvo M, Demirer T, Dini G, Einsele H, Gratwohl A, Madrigal A, Niederwieser D, Passweg J, Rocha V, Saccardi R, Schouten H, Schmitz N, Socie G, Sureda A, Apperley J; for the European Group for Blood and Marrow Transplantation: Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: definitions and current practice in Europe. *Bone Marrow Transplantation* 2006; 37:439–449
- G. Grazzini & S. Pupella
National Blood Centre
Giano della Bella n 27
E-mail: direzione.cns@iss.it
- A. Nanni Costa & L. Lombardini
National Transplant Center
- A. Bosi
Italian Cooperative Group for Bone Marrow Transplantation
- N. Sacchi
Italian Bone Marrow Donors Registry
- L. Lecchi & P. Rebulli
Milan Cord Blood Bank

E. D. Calderón Garcidueñas

Question 1

In Mexico, there are three public cord blood banks: CordMX Centro Nacional de Transfusión Sanguínea (CNTS) health ministry, La Raza Cord Blood Bank IMSS at Mexico City and Hospital Universitario de Nuevo León Cord Blood Bank at Monterrey Nuevo León.

Only CordMX Cord Blood Bank is part of a national and international network. CordMX is an associated member of NetCord (<http://www.netcord.org/>) since 2006. The health ministry is the authority responsible for these cord blood banks, through the CNTS (<https://www.cnts.salud.gob.mx/>) and the Comisión Federal para la Protección contra el Riesgo Sanitario (<http://www.cofepris.gob.mx/>).

The CordMX offers the opportunity to store allogeneic related cord blood (directed) only in case a patient is a candidate for transplantation and the mother is already pregnant. This service must be required by the transplant centre. CordMX do not offer the opportunity to store autologous cord blood samples.

Question 2

Yes, CordMX agrees that some conditions treatable with allogeneic cord blood are already present in the stem cells of the infant and that therefore such conditions should be treated with allogeneic rather than autologous cord blood.

In reference to the storage of samples of autologous cord blood, we think that it can be allowed but it should not be encouraged.

The principal problem with autologous cord blood banks in Mexico is that in most of the private cord blood banks the units are not tested in accordance with international standards, thus 100% of the recollected units are stored, but half of these units are not fit for transplantation.

If, for some reason, somebody needs to store autologous cord blood, it should be stored in a non-for-profit bank.

In Mexico, there are about 16 commercial banks to store autologous blood samples. As there is no national law that regulates these banks, they work only with a sanitary licence emitted by the Ministry of Health (Comisión Federal para la Protección contra el Riesgo Sanitario). These commercial banks do not apply the NetCord international standards.

Question 3

CordMX considers that there are no indications for autologous storage. For related storage, only in the case of patients with oncology and a disease not requiring bone marrow transplantation, and their mother has a healthy pregnancy.

E. D. Calderón Garcidueñas
Subdirectora de Investigación
CordMX BSCU

Centro Nacional de la Transfusión Sanguínea
Othón de Mendizábal No. 195
Colonia Zacatenco
México D.F. 07360
E-mail: evadel@servidor.unam.mx

J. M. van Beckhoven, H. J. C. de Wit, W. E. Fibbe *et al.*

Question 1

In the Netherlands, anonymous allogeneic cord blood units are collected, tested and stored in a national cord blood bank under the responsible authority of Sanquin, the Dutch blood supply institute, a not-for-profit organization supervised by the Ministry of Health. The Sanquin cord blood bank has a standing agreement with two other Dutch foundations, Europdonor and EuroCord. Europdonor is the national unrelated stem cell donor bank and hub centre, responsible for making the ca. 3600 Dutch cord blood transplants available for search in BMDW and holding contacts with the transplant centres for selection and delivery arrangements. EuroCord Nederland is represented in NetCord/FACT and participates in international platforms for qualifications and the medical use of cord blood transplantation.

The Dutch cord blood bank also acts as intermediary for the collection and storage of cord blood from relatives intended for allogeneic related transplantation. Guidelines for indications are periodically provided by the Dutch societies of Paediatrics and Haematology and the cord blood bank only accepts these directed cord bloods on request of the treating physician of the potential recipient. The costs associated with related cord blood storage are reimbursed by the health insurance of the patient or by the search budget of the transplant centre. For autologous cord blood storage, there are no procedures and no facilities in the country, although every hospital running an accredited stem cell laboratory can collect and store directed and autologous cord blood units for its own use.

Question 2

We do agree that some conditions treatable with allogeneic cord blood might be present in the infant's stem cells. The Dutch cord blood bank EuroCord Nederland excludes cord blood when certain hereditary diseases are present in the family, or in the case of leukaemia in first- and second-line relatives. The cord blood from relatives is only used for directed donation on request of the transplant centre.

There are no public or private banks for autologous cord blood in the Netherlands, but some Belgian private banks do operate in our country. The issue of the storage of autologous cord blood, lacking the prospect of a specific treatment intention in the public bank, is under debate in our country.

If scientific evidence will emerge that autologous cord blood may serve as a tool for the repair of haematopoietic or degenerative diseases for which the current treatment is already covered by health insurance, accessible to all civilians, it is obvious that the not-for-profit cord blood bank is the designated organization for autologous cord blood collection and storage, fulfilling all quality regulations. For indications lacking a scientific basis, there is poor ground for using public money for the storage of autologous cord blood. However, for civilians who express, despite state of art information as

required by the CoE 2004/23, a strong desire to have access to stored autologous cord blood at their own expense, the decision to combine private and public banking has not yet come to conclusions. Many obstacles have to be overcome, among others the policy of the Dutch blood supply to offer expertise and facilities for autologous use of blood products solely on medical indications.

If, on the other hand, private cord blood banks will be established, we assume that quality requirements will be in accordance with the law on safety and qualification of human cells, controlled by the National Health Inspection. Permission from this authority is also required for the import of autologous cord blood from Belgium (or other countries). As far as we are informed, autologous cord blood has not yet been imported or used.

Question 3

Currently, as mentioned above, the Dutch cord blood bank accepts directed cord blood intended for allogeneic use on the request of a physician of a transplant centre. Indications include haemato-oncological diseases and hereditary diseases that can also be treated by allogeneic related or unrelated stem cells from adult donors. If after HLA-typing and additional investigations for the absence of the hereditary disease the donor is declared unsuitable for directed use, the product can only be used for research, because EuroCord Nederland standards do not allow these donations for unrelated use. For autologous cord blood storage, indications do not exist and if such indications emerge, they are best integrated in the not-for-profit cord blood bank.

Close monitoring of scientific progress about repair by autologous cord blood stem cells is a joint responsibility of several experts in order not to miss opportunities for future patients.

J. M. van Beckhoven
SanquinSouthwest Region
Sanquin Cordblood Bank
Plesmanlaan 1b
2333 BZ Leiden
the Netherlands
E-mail: j.vanbeckhoven@sanquin.nl

H. J. C. de Wit
Sanquin
1006 AN Amsterdam
the Netherlands
E-mail: hjc.dewit@sanquin.nl

W. E. Fibbe
EuroCord Nederland
Leiden University Medical Center
Department of Haematology
Location C2R – Room 137
2333 AA Leiden
the Netherlands
E-mail: w.e.fibbe@lumc.nl

A. Brand
Eurodoner
Plesmanlaan 1b
2333 BZ Leiden
the Netherlands
E-mail: a.brand@sanquin.nl

E. B. Zhiburt

Question 1

In Russia, three non-for-profit cord blood banks exist in Moscow, Samara and Kazan. At present, they are not part of national or international network. The Moscow and Samara cord blood banks are in the process to join EuroCord/NetCord. Regional governments are responsible for these cord blood banks. So far, the banks have only collected cells while no transplantations have yet been performed.

Question 2

Six commercial banks to store autologous cord blood samples already exist in Russia (Hemabank, Moscow; Cryocenter, Moscow; Flora-Med, Moscow; Pokrovsky stem cells bank; Saint-Petersburg; Hemabank, Saint-Petersburg; and Trans-Technologies's, Saint-Petersburg).

All the banks are licenced by the federal health control service. There is no authority responsible for these banks. Sometimes stem cells are insured by a private insurance company.

Hemabank (Moscow) has one example of successful (4 years ago) allogeneic cord stem cells transplantation from a younger brother to treat neuroblastoma.

Question 3

The indications are quite common. Family anamnesis of malignant and hereditary diseases may be an indication to store directed (related and/or autologous) cord blood samples.

E. B. Zhiburt
Head Transfusionist
Pirogov Russian National Medical Surgical Center
65, Nizhnyaya Pervomaiskaya ul.
Moscow, 105203
Russia
E-mail: ezhiburt@yandex.ru

T. Bart, for the Swisscord Commission

Question 1

In Switzerland, there are two non-for-profit cord blood banks, one in Basel and one in Geneva, in which cord blood units are stored for allogeneic transplantation.

These two public banks are operated under the responsibility of the departments of haematology together with the departments of laboratory medicine and gynaecology of the university hospitals of the respective cities and under

the surveillance of the national regulatory authority (Swiss Institute for Therapeutic Products/Swissmedic). The respective cord blood banks are in charge of processing and storage of cord blood products.

The Swiss national blood stem cell donor registry (Swiss Foundation Blood Stem Cells) is – as in the case of adult blood stem cells – in charge of all activities related to national and international exchange of cord blood products destined for transplantation. Its specialist commission Swisscord, consisting of representatives of the registry as well as specialists in haematology, gynaecology, laboratory medicine and blood transfusion, decides upon policies and other medical-related activities in public cord blood banking and cord blood transplantation.

As regards directed cord blood banking, the banks offer the possibility of directed banking in case there is a sibling of the newborn with a disease that can be treated by allogeneic HSCT.

Question 2

A well-matched allogeneic cord blood unit is usually preferable to an autologous cord blood unit not only because of the potential presence of malignant or premalignant stem cells, but also because of the potential of a graft versus leukaemia effect. Therefore, cord blood banks should provide cord blood units with a large choice of HLA phenotypes and haplotypes and autologous cord blood storage should not be promoted actively.

The potential conflict of interest between commercial and non-for-profit banks should be seriously taken into consideration upon the decision to store autologous cord blood units in the same cord blood bank as allogeneic cord blood.

A commercial organization operating in this field should be responsible for its own activity and products. It has to be assured that an equivalent quality control as it is applied upon public banks for allogeneic products should be in force.

There are at least three or four commercial firms active in the storage of autologous blood samples to our knowledge.

Swissmedic is responsible for these banks.

The quality control of such blood banks is assured by the regulatory authority (Swissmedic), which begins to run inspections, to our knowledge.

These banks are only involved in storing autologous cord blood units, to our knowledge.

Question 3

The indications for storing directed cord blood samples should be the same as those for allogeneic stem cell transplantations.

T. Bart
Chief Operating Officer
Swiss Blood Stem Cells
Laupenstrasse 37
CH-3001 Bern
Switzerland
E-mail: thomas.bart@bloodstemcells.ch

M. Beksac

Question 1

Cord blood is a source of stem cells since 1995 in Turkey. However, the indications are limited: it is used mainly for paediatric patients who do not have an HLA-identical sibling and need an allogeneic stem cell transplantation urgently [1]. For patients who can afford to wait until the matched sibling is grown up to the age of donation, paediatric transplant teams prefer to use bone marrow for transplantation and keep the cord blood as a backup. During the last 2 years, unrelated cord blood transplants have become a frequent treatment for both paediatric and adult patients. For patients who lack a family donor and carry rare HLA haplotypes, unrelated cord blood is a life-saver. As elsewhere, the percentage of cord blood among unrelated paediatric transplants is also approaching 50% in our country [2].

For these reasons, in Turkey, cord blood collection and storage was initiated in accredited academic institutions where autologous stem cell, either bone marrow or stem cell, collection and storage are standardized procedures. There are only five active cord blood banks that collect cord blood for allogeneic purposes. With the exception of one, these are all located in academic institutions and are non-for-profit organizations. These banks do not belong to a national or an international network yet. One of the academic allogeneic cord blood banks gave start to the first unrelated cord blood banking activity in Turkey in 2004. TR1CB is recognized by BMDW and is listed on the website.

There is a national regulation prepared and run under the directory of the Ministry of Health on cord blood banking. This regulation defines the criteria for national accreditation and audit of private banks who plan to collect and store autologous cord blood. It requires a minimum of 25% allogeneic cord blood storage at private banks. A national advisory board of experts appointed by the Ministry of Health for 1-year term fulfils the decision-making requirements defined by the regulation. Since the institution of this regulation in 2005, only one bank has been able to get a certificate from the Ministry of Health. There are at least five cord blood banks who have applied for approval and are under evaluation.

In Turkey where the birth rate is still higher than in many countries, autologous private cord blood banking boomed in early 2000s. However, both the Ministry of Health and medical organizations led by mainly haematologists and obstetricians prevented illegal banking activities that purely aimed at financial gains and did not meet medical or scientific requirements. The Turkish Society of Hematology has addressed the public by many means including advertisements in daily newspapers to prevent private cord blood banks from misleading people by inaccurate information on the need of autologous storage.

Question 2

As stated recently by the American Society of Blood and Bone Marrow Transplantation, the chances for a need for autologous cord blood in general are so low that it can be neglected [3]. Furthermore, autologous adult stem cells can be obtained from various tissues. The current medical practice does not involve the use of such autologous cells for the treatment of aplastic anaemia or leukaemia for which allogeneic stem cell transplantation offers a long-term cure. Numerous reports on the very early detection of leukaemic cells in the prenatal life many months preceding the diagnosis of paediatric postnatal leukaemia hinders the use of autologous cord blood. Moreover, graft versus leukaemia is a proven benefit of allogeneic transplantation and is much less evident with autologous cells [3].

Acquired aplastic anaemia may be the only condition in which storage of unaffected autologous cord blood can be a life-saver. It is also important to mention that the probability of aplastic anaemia is approximately 1 in 10 000 and can be cured by means other than autologous cord blood, that is, HLA-matched stem cells from family members or unrelated donors [3].

Cord blood is a useful source of stem cells. The major limitation is that the number of stem cells is sufficient for only small sized recipients and that there is a delay in engraftment. Another weakness is the lack of the capacity of a strong immune response. Thus, the question that we are trying to answer is not only a qualitative comparison between allogeneic cells vs. autologous cells, from which for almost all situations allogeneic cells win, but also involves the quantitative sufficiency of cord blood as well. If cord blood is stored in facilities accessible to all those in need in a non-profit fashion, the need for autologous storage will diminish. This will spare a waste of cord blood resulting from many years of storage without a necessity for use in the owner while it could have been used for a subject who has a disease that could be treatable with these cells. It is also important and should not be forgotten that once the owner is above a certain weight, usually 20–30 kg, depending on the number of stem cells present in his cord blood [4], it will not be sufficient for a stem cell transplantation and the benefits of cord blood stem cells for long-term treatment of degenerative diseases of the elderly is still an ongoing debate.

We recommend that cord blood should be stored in allogeneic/altruistic facilities that are non-profit organizations and are open to access.

In an ideal world in which all cord bloods in the depository are available, depending on the need defined by HLA frequencies, cell content, blood group, etc., there will be no need for separate banks for autologous cord blood banking. The management of altruistic cord blood banks must be performed locally. However, accreditation by national and international authorities must be encouraged. All banks must

abide to standards defined by international organizations. Thus, such cells can be transportable without any concerns about their quality or ethics.

Currently, there is only one private cord blood bank, which is a joint organization of a university hospital with a private sector and has received the cord blood certificate from the Ministry of Health. Unfortunately, the private autologous cord blood banks that were active before the institution of the national regulation in 2005 continued storage despite the lack of certification by the national authority. Some have transported cord blood to other countries in the past, although it is against the law. Some of these banks have submitted their application and approval is expected to follow.

The Ministry of Health is responsible for these banks.

The regulation of 2005 enforces these banks to comply with the GMP requirements. The advisory board and the GMP inspectors of the ministry ensure that the banks fulfil these criteria. Control of quality assurance and management is maintained by continuous audits.

The regulation mandates that at least 25% of the cord blood stored in the bank is allogeneic. Usually the academic allogeneic cord blood banks are sufficient for this purpose and there is hardly a need for storage in private banks. Even if the families accept donation for altruistic purposes, stem cell quantification and HLA-typing costs are limiting factors in such conditions.

Question 3

From the mid-1990s, when allogeneic cord blood transplantation became available in Turkey, thalassaemia is the number one indication that is followed by acute lymphoblastic leukaemia in second remission or first remission with poor prognostic features and acute myelogenous leukaemia. As prenatal diagnosis of thalassaemia is widely applicable in our country, prenatal or postnatal HLA typing has guided us in the decision making of cord blood storage for directed purposes. A complete HLA-match based on molecular HLA-A, -B, -C and -DRB1 typing is required for the storage of allogeneic cord blood for either benign or malignant disorders. For patients who have an HLA-identical sibling cord blood timing of transplantation and use of cord blood must be made by the paediatric transplant team. Due to limitations in storage capacity, one haplotype-matched allogeneic cord blood can be discarded unless the stem cell content is very high. If altruistic banking is available, cord blood from siblings proven not to carry the disease can be stored regardless of the HLA-match degree. For directed cord blood collection and storage, paediatricians must publish and update the list of diseases treatable with stem cell transplantation. Such lists are currently available [3]. Treatment of adult disorders including diabetes, Alzheimer's and Parkinson's disease is certainly not among the list of indications.

In some situations when a patient is in need of a transplantation and no family donor is found, assisted *in vitro* fertilization and selection of embryos with HLA-match have led to successful pregnancies and transplantation. However, such an approach involves many ethical concerns and conflicts.

In situations in which diseases treatable with stem cell transplantation are frequent within the family or are expected to occur more frequently than in the general population, autologous cord blood can be stored depending on the decision of the relevant physicians and paediatricians including geneticists. However, currently such situations are extremely rare and are expected to be higher in families with consanguineous marriages.

References

- 1 Miniero R, Rocha V, Saracco P, Locatelli F, Brichard B, Nagler A, Roberts I, Yaniv I, Beksac M, Bernaudin F, Gluckman E: Cord blood transplantation (CBT) in hemoglobinopathies. *Eurocord. Bone Marrow Transplant* 1998; 22 (Suppl. 1):S78-79
- 2 Gluckman E, Rocha V, Beksac M, Zintl F: European results of unrelated cord blood transplants. *Bone Marrow Transplantation* 1998; 21 (Suppl. 3):S87-S91
- 3 Ballen KK, Barker JN, Stewart SK, Greene MF, Lane TA; American Society of Blood and Marrow Transplantation: Collection and preservation of cord blood for personal use. *Biol Blood Marrow Transplant* 2008; 14:356-363
- 4 Beksac M, Dalva K, Arat M, Beksac S: Fetal-obstetric parameters that decrease volume (V) or mononuclear cell content (MNC) do not influence total hematopoietic cell content (HSCC) in the cord blood (CB) harvest. *Blood* 2003; (Suppl. 1):5399a

M. Beksac

Ankara University Cord Blood Bank

Ankara Tıp Fakültesi Hematoloji B.D.

Cebeci yerleskesi

Ankara 06620

Turkey

E-mail: beksac@medicine.ankara.edu.tr

C. Navarrete & F. Regan

Question 1

Currently, there are two non-for-profit cord blood banks in the UK storing samples for clinical use, the National Health Service Cord Blood Bank (NHS CBB) (formerly the London Cord Blood Bank) [1] and the Northern Ireland (NI) Cord Blood Bank. The units from these two cord blood banks are registered with the British Bone Marrow Registry (BBMR) for national searches and through the BBMR with the BMDW Registry for international searches. In addition, all the units from the NHS CBB, which is NetCord/FACT accredited, are also listed with NetCord.

The National Health Service Blood and Transplant authority is responsible for the NHS CBB and the Northern Ireland Blood Service is the authority responsible for the NI units.

The NHS CBB also runs a national programme to collect related (directed) cord blood units for patients with a variety of conditions including malignant and non-malignant disorders, such as acute and chronic leukaemia, haemoglobinopathies and immunodeficiencies. However, the majority of the units went to patients with non-malignancies [2]. The request for these collections is initiated by the treating physician and requires the consent of the obstetrician responsible for the delivery of the baby. The NHS CBB is not involved in the collection of autologous units.

Question 2

There is evidence that preleukaemic mutations can be present in the cord blood of babies who develop leukaemia years later [3]. We are aware therefore that many transplant physicians would not wish to use autologous cord blood, but would choose an allogeneic source of stem cells in preference. Autologous cord blood could be stored in case a sibling should ever develop a disease requiring a cord blood transplant and in the hope that the cord is a suitable match. However, the chances of the stored cord blood being used are low (estimates vary between 1 in 1400 to 1 in 20 000) [4]. Many transplant physicians would prefer, if possible, to wait until the cord donor child has grown a little, then procure bone marrow as a source of a larger dose of stem cells. Autologous cord blood could be stored for the future as a source of multipotent mesenchymal stem cells for potential use in regenerative medicine (e.g. to treat cardiac or neurological disease). There is some evidence of progress in using these in animal experiments and some early trials are underway in humans, but it is too early to draw conclusions about clinical effectiveness of these cells. Furthermore, it is not yet clear which is the optimal source of these cells and at present these cells be obtained from several sources including bone marrow, cord blood or cord matrix (Wharton's jelly) [5]. The viability of the haematopoietic or mesenchymal stem cells stored for decades, until the appearance of diseases that might require their use, is not currently known. On balance, we conclude that there is not at present sufficient evidence to justify or indeed promote the storage of autologous cord blood.

If autologous cord blood is collected, it could in principle be stored in a non-for-profit bank alongside allogeneic cord blood donations. Indeed, one advantage might be that privately funded autologous donations could help to financially support the allogeneic cord bank. However, to ensure the microbiological safety of the allogeneic units stored, either the autologous units would have to be subject to the same microbiological testing and the same degree of donor questioning for risk factors for infectious diseases (to minimize the risk of 'window period' infections), in order to minimize the risk of transmission during storage, or the autologous units would need to be reliably segregated from the allogeneic units. Apart from the issue of storage in the same bank, if the

same collection staff were used to approach donors for allogeneic and autologous units, there would be a potential conflict of interest in terms of which form of donation the collectors would encourage the donors to choose. On balance, separate storage of autologous and allogeneic cord blood donations would be preferable.

Cord blood banks for storing autologous donations should be subject to the same national and international regulations and accreditation schemes that are applicable to the cord blood banks storing allogeneic donations. These include: NetCord/FACT *International Standards for Cord Blood Collection, Processing, Testing, Banking, Selection and Release* [6], EU Directive 2004/23/EC on setting standards for quality and safety in the donation, procurement, processing, preservation, storage and distribution of human tissues and cells [7], Human Tissue Act [8] and the Food and Drug Administration *Eligibility Determination for Donors of Human Cells, Tissues and Cellular and Tissue-Based Products* [9]. Inspections with a view to accreditation aim to determine that appropriate quality assurance systems are in place.

In the UK, several commercial banks store autologous cord blood (<http://www.parentsguidecordblood.com/content/usa/banklists/summary.shtml#uk>). They need to be MHRA accredited and need to comply with the Human Tissue Act and EU Directive and can voluntarily apply for NetCord/FACT accreditation.

Question 3

Same as answer to Question 1 for directed donations. For autologous donations, we cannot comment on appropriate indications – see answer to Question 2.

References

- 1 Davey S, Armitage S, Rocha V, Garnier F, Brown J, Brown CJ, Warwick R, Fehily D, Watt S, Gluckman E, Vora A, Contreras M, Navarrete C: The London Cord Blood Bank: Analysis of banking and transplantation outcome. *Br J Haematol* 2004; 125:358–365
- 2 Smythe J, Armitage S, McDonald D, Pamphilon D, Guttridge M, Brown J, Green A, Warwick RM, Lankester A, Fehily D, Contreras M, Navarrete C, Watt SM: Directed sibling cord blood banking for transplantation: the ten year experience in the National Blood Service in England. *Stem Cells* 2007; 25: 2087–2093
- 3 Greaves MF, Wiemels J: Origins of chromosome translocations in childhood leukaemia. *Nat Rev Cancer* 2003; 3:1–11
- 4 European Group on Ethics in Science and New Technologies: *Ethical Aspects of Umbilical Cord Blood Banking*. Strasbourg, European Commission, 2004; available at www.who.int/ethics/en/ETH_TissueBanking.pdf
- 5 Manca MF, Zwart I, Beo J, Rajanathanan P, Ling-Sun J, Navarrete R, Girdlestone J, Navarrete C: Characterization of mesenchymal stromal cells derived from full term umbilical cord blood. *Cytotherapy* 2008; 10:54–68
- 6 NETCORD-FACT: *International Standards for Cord Blood Collection, Processing, Testing, Banking, Selection and Release*, 3rd edn, 2006; available at http://factwebsite.org/uploadedFiles/Standards/CB%20Stds_3rd%20Ed_FINAL%201%2029%2007.pdf
- 7 Directive 2004/23/EC of the European Parliament and of the Council of 31st March 2004 on setting standards for quality and safety in the donation, procurement, processing, preservation, storage and distribution of human tissues and cells. *Official Journal of European Union* 2004; 07/04/2004:L 102/48–L 102/58.
- 8 Human Tissue Act 2004. London, UK, HMSO; available at http://www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_1
- 9 Food and Drug Administration: *Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/PS)*. Rockville, MD, Food and Drug Administration; available at <http://www.fda.gov/cber/gdlns/tissdonor.pdf>

C. Navarrete
Consultant Clinical Scientist & Scientific Director
NHS Cord Blood Bank
NHS Blood & Transplant
Colindale Avenue, London
NW9 5BG
UK
E-mail: cristina.navarrete@nbs.nhs.uk

F. Regan
Consultant Hematologist & Medical Director
NHS Cord Blood Bank
NHS Blood & Transplant
Colindale Avenue, London
NW9 5BG
UK
E-mail: fiona.regan@nbs.nhs.uk