REVIEW ARTICLE

Stem Cells Derived From Cord Blood in Transplantation and Regenerative Medicine

Verena Reimann, Ursula Creutzig, Gesine Kögler

SUMMARY

Background: Physicians of any specialty may be the first persons to whom prospective parents turn for information about the acquisition and storage of stem cells derived from cord blood. Stem cells can potentially be used to treat many diseases, yet they are not a panacea. This article provides an overview of their current and possible future applications.

Methods: Original papers were retrieved by a selective search of the literature, and the Internet sites and advertising brochures of private stem cell banks were also examined.

Results: Allogeneic hematopoietic stem cells derived from umbilical cord blood (obtained from healthy donors, rather than from the patient to be treated) have been in routine use worldwide for more than ten years in the treatment of hematopoietic diseases. Experiments in cell culture and in animal models suggest that these cells might be of therapeutic use in regenerative medicine, but also show that this potential can be realized only if the cells are not cryopreserved. There is as yet no routine clinical application of autologous hematopoietic stem cells from cord blood (self-donation of blood), even though cord blood has been stored in private banks for more than ten years.

Conclusions: Autologous stem cells from cord blood have poor prospects for use in regenerative medicine, because they have to be cryopreserved until use. Physicians should tell prospective parents that they have no reason to feel guilty if they choose not to store cord blood in a private bank.

Key words: stemcell therapy, blood products, adult stem cells, hematopoietic stem cells, allogeneic transplantation

Stem cell research—including the possibility of reprogramming somatic cells (1, 2)—is a rapidly developing albeit controversially discussed scientific subject matter. The facts and circumstances are complicated and subject to perpetual change as a result of new scientific insights; in normal circumstances, parents-to-be are unable to fully comprehend these with all their implications. Such expectant parents are vulnerable with regard to the future of their unborn children and are keen to provide any kind of health provision for their offspring. It is therefore very easy for those running private stem cell banks to create the impression that it is a fundamental mistake not to store umbilical cord blood. This article aims to help doctors to inform parents-to-be comprehensively about the curative potential of stem cells derived from cord blood.

Methods

We conducted a selective literature search in the PubMed database. We used the search terms “cord blood”, (“non-hematopoietic/mesenchymal/unrestricted”) “stem cells”, “transplantation”, “commercial/private cord blood bank/banking (CBB)”, “diabetes type I”, “cardiovascular disease/tissue engineering”, “heart valves”, “iPS cells”, “ischemia”, “leukemia”, “neural differentiation”, “regenerative medicine”, “airway transplantation”, and “stroke”.

Additionally, we conducted an internet search using the search terms “Nabelschnurblut” (*cord blood*), “Nabelschnurbluteinlagerung” (*cord blood storage*), “Schwangerschaft” (*pregnancy*), and “Stammzellen” (*stem cells*).

Use of stem cells from umbilical cord blood

Hematopoietic stem cells from “allogeneic” cord blood donations (“allogeneic donations,” obtained from healthy donors, rather than from the patient to be treated) from public cord blood banks have been successfully used in the treatment of more than 70 indications for more than 15 years because they can be cryopreserved and unfrozen without undergoing any substantial loss of function. Such hematopoietic stem cells have been used in the treatment of (3, 4):

- Malignancies of the hematopoietic and lymphatic systems
- Metabolic disorders
- Immunodeficiencies
- Tumors

Cite this as: Dtsch Arztebl Int 2009; 106(50): 831–6
DOI: 10.3238/arztebl.2009.0831

Institut für Transplantationsdiagnostik und Zelltherapeutika, José Carreras Stammzellbank, Universitätsklinikum Düsseldorf: Dr. rer. medic. Reimann, Prof. Dr. rer. nat. Kögler

Gesellschaft für pädiatrische Onkologie und Hämatologie: Prof. Dr. med. Creutzig

GLOSSARY

- **Allogenic**
 - Donor and recipient of a transplant are not identical (they may be related or not related)
- **Autologous**
 - Donor and recipient are identical
- **Graft**
 - Transplant
- **Hematopoiesis**
 - Formation of blood
- **Graft versus leukemia (GVL) effect**
 - Desired immunological attack of the stem cell transplant on the leukemia cells
- **Graft versus host disease (GVHD)**
 - Complication of stem cell transplantation whereby the lymphocytes contained in the transplant mount an attack on the recipient's body. GVHD can vary in degree/extent and can result in a patient's death. Normally it can be treated by administering immunosuppressants.

- Hemoglobinopathies
- Genetic defects.

Since the first ever cord blood transplantation (5), allogeneic cord blood has been used in more than 9300 cases (*eTable*) (www.netcord.org/Archive/Charts/Inventory_March_09.gif). Worldwide, more than 200 000 cryopreserved allogeneic transplants are available, which can be ordered via central cord blood stem cell donor registries. The number of patients who have received transplantations of allogeneic cord blood is continually rising worldwide. In Germany in 2008, for the first time, more adults received transplants than did children.

Advantages and disadvantages

Umbilical cord blood is much more readily available than bone marrow—in an emergency situation, transplants can be provided within two working days. Because of the immunological immaturity of the cells, cord blood is better tolerated than bone marrow while being just as safe and effective (6, 7). In certain circumstances, cord blood can be transplanted successfully even if the donor and the recipient are not a perfect match; this substantially widens the range of patients who are able to receive a transplant (7). The lower total number of cells compared to bone marrow would be a disadvantage (7, 8) if it were not compensated for by the use of duplicate transplantations (simultaneous transplantation of two matching transplants for one patient).

For a population of about 60 million, an allogeneic stem cell bank statistically requires an inventory of 50 000 allogeneic transplants in order to provide a matching (albeit not a 100% match) transplant for 96%

of patients (9). Establishing allogeneic stem cell banks of such a size is not possible without financial support. Such funding is desirable because it is especially the extremely rapid availability of cord blood transplants that saves the lives of patients with acute leukemia, and rapid allogeneic stem cell transplantation notably increases survival in prognostically unfavorable risk constellations (7, e30).

Use in regenerative medicine

Fresh (that is, not previously frozen) cord blood is a promising source of non-hematopoietic stem cells. Among others, it contains endothelial cells, mesenchymal stromal cells (MSC), and unrestricted somatic stem cells (USSC) (10–14). Non-hematopoietic stem cells are scarce in fresh blood and are not detectable to a sufficient degree after cryopreservation/unfreezing (15). Generating clinically relevant volumes of non-hematopoietic stem cells is therefore possible in an efficient manner only by using fresh materials. Under conditions of Good Manufacturing Practice (GMP) USSC from fresh cord blood can be multiplied quite easily. In theory, USSC can be amplified to a cell number of 10^{15} and differentiated into different tissues in vitro and in vivo (osteoblasts, cartilaginous cells, endodermal and neuronal cells) (10–12, 15). These cells offer a realistic perspective for tissue regeneration. The statement that nowadays even replacement organs are being developed by using stem cells might be misunderstood to mean that functional organs are being grown from stem cells even now. However, this type of autologous use as standard therapy is strictly in the distant future. We have selected some examples to explain the potential that stem cells from fresh cord blood currently do have.

Myocardial infarction

Cell cultures and animal experiments have shown that stem cells from fresh cord blood can alleviate the effects of heart attacks. They migrate to the area of the infarction, reduce the size of the infarction, improve cardiac function, and increase capillary density. In vitro, non-hematopoietic cord blood stem cells differentiate into myocardial cells (16); however, this has not been observed in vivo. The fact that the size of the infarction is reduced in vivo probably indicates a mechanism of action via cytokine release (17). Large animal models will show the extent to which the data gleaned from small animal experiments can be reproduced (18). Autologous stem cells from bone marrow are already being used in clinical practice in order to minimize sequelae after myocardial infarction (15, 19). Mechanisms of action under discussion in this context also concern cytokine release. Cord blood has thus far not been used to treat myocardial infarction in humans.

Heart valve replacement

In rare cases, children with congenital heart valve defects require an entirely new cardiac valve. For this purpose, a donor valve can be stripped completely of

cells and implanted. Studies over 5 years have shown that such decellularized heart valves in children grow in parallel to the respective child's bodily growth (20, 21). Some working groups are planning to colonize these heart valve structures with autologous cord blood stem cells, endothelial cells (including endothelial cells from cord blood), cells from umbilical cord vessels, or MSC (from bone marrow or cord blood) and are hoping that this procedure will bring further improvements to the clinical situation (22, 23). Owing to the extremely high organizational and financial expense, however, it is to be expected that there will be only few centers that specialize in generating such cells from fresh cord blood and to process these in a manner that complies with the German Medicines Act.

Bronchial reconstruction

The revolutionary example of the reconstruction of a bronchus by means of implanting a donated and decellularized trachea highlights the fact that cells of different origin (tracheal epithelial cells and cartilaginous bone marrow cells) are required for the purposes of tissue reconstruction (24).

Diabetes mellitus

Two studies with different therapeutic approaches are currently investigating the influence of cord blood stem cells on improving the function of pancreatic beta cells. In the first approach, children with young-onset diabetes are infused with autologous cord blood without chemotherapy (25). Initial results have shown that such autologous cord blood transplantation without preceding chemotherapy has not resulted in any adverse effects but has not significantly improved the situation either. All children are still dependent on administration of insulin. In the second approach, adult patients with newly diagnosed diabetes mellitus underwent non-myeloablative chemotherapy after receiving reinfused stem cells from autologous bone marrow (e1). It has come in for strong criticism that the subjects were exposed to the risk of chemotherapy (e2). Some patients were not dependent on insulin at the time of follow-up, but it is not clear whether this effect was temporary. Final results are awaited for both studies.

Neurological disorders

Under certain conditions, stem cells from fresh cord blood are able to differentiate into neurons, microglial cells, and astrocytes. For neurological disorders, animal models have shown that treatment with fresh cord blood resulted in improvements in the progression of disorders including stroke, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, and spinal cord injuries. Further, improved bone healing was noted (15).

Stroke—Rats were subjected to a MCAO (middle cerebral artery occlusion) procedure. After subsequent infusion of human cord blood, behavior tests were conducted. The animals that had received the cord blood displayed significantly better reactions than the

TABLE

Summary of table 1 of the European Group for Blood and Marrow Transplantation (EBMT) Survey 2006 (e26)

Total number of stem cell transplants in Europe in 2006	25 050
Allogeneic transplants	9661
Of which related and unrelated bone marrow and PBSC	9154
Of which related and unrelated umbilical cord blood transplants	507
Autologous transplants	15 389
Of which bone marrow in isolation	256
Of which bone marrow and PBSC	15 133
Of which autologous umbilical cord blood	0

control groups without cord blood, independent of the dosage (e3).

Amyotrophic lateral sclerosis (ALS)—In the mouse model, administration of human cord blood slowed progression of ALS and prolonged survival of the mice (e4).

Parkinson's disease—The Parkinson mouse model yielded similar results. The control animals did not receive any cord blood and developed the disease and died significantly earlier than the animals that had been treated with cord blood (e5).

Alzheimer's disease—The Alzheimer mouse model similarly showed slowed disease progression, a prolonged survival interval, and a clear reduction of the disease-typical beta-amyloid plaques in the brain after the administration of human cord blood (e5, e6).

Spinal cord injuries—In the rat model, infusion of cord blood after spinal cord injuries resulted in improved behavior patterns (e7).

Infantile cerebral palsy and other cerebral impairments—A study from Duke University (Durham, North Carolina) is currently investigating the extent to which administration of autologous cord blood influences disease progression in children with infantile cerebral palsy or other cerebral impairments (for example, as a result of oxygen deprivation during birth). The plan is to treat a total of 40 children with their own, previously stored, cord blood and follow their development over two years. Initial studies have shown promising results, but it is unclear what caused these. The efficacy can be shown only by means of a controlled study (Kurtzberg in [7]).

Reprogrammed somatic cells

Reprogrammed somatic cells, so-called induced pluripotent stem (iPS) cells, harbor an enormous potential in the context of regenerative medicine, because they have some of the attributes of embryonic stem cells. iPS cells can be generated from somatic cell lines of different origin, including dermal fibroblasts. All adult cell lines of a fully grown organism have one thing in common: The cellular systems, especially the mitochondrial DNA, are aged. For many years now,

mitochondria have been regarded as mainly responsible for cell aging and the development of age associated diseases. It therefore seems very useful to try to generate iPS cells from cord blood because such cells are young and have not yet accumulated any damage (1).

Recently, two working groups have succeeded in generating iPS cells from cord blood by using viral vectors. This is one method of producing cells of an “embryonic stem cell character” (including teratoma formation) from cord blood (e31). This approach is ideally suited for the purposes of research and drug screening, but it does not provide any clinical options. Only once iPS cells have been successfully created without using viral vectors and without teratoma formation can their clinical use even be considered under the implementation of the German Medicines Act [*Arzneimittelgesetz*] might even be considered e31).

We therefore summarize as follows:

- Allogeneic—that is, not for use in the patient they originated from—stem cells from cord blood are excellently suited to treating disorders of the hematopoietic system.
- MSC, USSC, and endothelial cells in the amounts that are required for therapeutic use can be generated only from fresh—not previously frozen—cord blood.

However, in disregard of this fact, some private providers’ statements may be misunderstood to mean that autologous use is almost imminent.

Private providers of cord blood banks

Privately run cord blood banks store cord blood for donors’ own use and keep this for a certain period of time, for a fee that the parents pay to the company. It is possible that the parents regard this service as a sort of “biological life insurance policy” for their children. However, a scientific rationale and an indication for the use of such services are thus far lacking.

The probability that a child’s life will one day depend on its own stored cord blood is extremely low. Of an estimated 2.5 million autologous donations stored worldwide, a maximum of 100 have been transplanted so far (including allogeneic transplants for siblings). The ratio of used to stored preparations is about 1:25 000 (e8, e9). The German association for bone marrow and blood stem cell transplantation (*Deutsche Arbeitsgemeinschaft für Knochenmark- und Blutstammzelltransplantation*, www.dag-kbt.de) states the following: “Mothers of healthy neonates and their families should know that according to the current state of knowledge it is not an oversight to not store the umbilical cord blood of the neonate. Those who wish to pursue this measure individually and finance it themselves should receive factual information and explanations about the currently speculative nature of such ventures. [...] It has to be guaranteed in any case that [...] pregnant women and their families receive independent information and explanations from other sources than commercial providers. It is vital—not only for medical reasons but also in the sense of consumer

protection—to prevent providers of stem cell banks from creating unrealistic expectations with their advertising claims that may cause unjustified moral conflict for parents.” Further renowned national and international medical organizations are currently clearly opposed to commercial umbilical cord blood banking (e10–e22).

The claims made by private cord blood banks are similar. Taken in isolation they are mostly correct, but in their totality they create the impression that cord blood is an essential and indispensable panacea, ready for use in regenerative medicine in the imminent future. The repeated claim that stem cells have been used for decades to treat cancers and blood disorders is undoubtedly correct, but in the overall context it may lead readers to conclude that autologous cord blood has this potential.

Autologous transplantation, including autologous cord blood transplantation, entail the risk of reverse transmission, something that is the case especially for childhood leukemias, some of which have a genetic origin (somatic mutations) (e23, e24). In autologous transplantation, the graft versus leukemia (GVL) effect (see *Glossary*) is lacking; this effect contributes crucially to preventing recurrences and is also lacking in identical twins, whose traits are 100% consistent. The absence of the GVL effect in this setting results in more frequent recurrences (e25).

One brochure advertising cord blood banking for donors’ own use mentions that more than 25 000 “stem cell transplantations” had been undertaken in Europe. This number is correct and may, for example, come from the EBMT Survey 2006, which, however, does not list autologous cord blood transplantation (*Table*).

The same brochure also mentions the first successful treatment of leukemia with autologous cord blood. In 2007, an autologous cord blood transplantation was performed in a child with a leukemia recurrence in the central nervous system (e27). However, this transplantation was merely an additional measure to try to reduce possible further recurrences in a very rare constellation.

According to the Internet and the daily press, cord blood stem cells are used in organ substitution/replacement, curing young-onset diabetes, and growing people’s third set of natural teeth. One statement on the web page www.nabelschnurblut-tv.de might be misunderstood to mean that cord blood counteracts cerebral damage and speech problems resulting from oxygen deprivation—the translated quote: “[...] This boy could be helped thanks to his parents’ foresight. Immediately after his birth they had stored his umbilical cord blood with a private provider. Only five days after the transplantation, Dallas spoke his first words [...]”.

For a while now, there has been an option of making the cord blood stored for one’s own use available to patients (“combined donations”). This means that on request the cord blood can be entered into a registry, but the blood remains the child’s property. Only where an

acute need for the blood arises the parents—or the child, if of age—decide whether to actually make the blood available. This seems positive at first glance, but in reality it means the following:

- The owner of the transplant would be forced to decide about a patient's life or death in an extreme case scenario; often cord blood becomes the option only if no other donor is available (e16).
- The decision about releasing the transplant is not on the hands of a medical professional.
- The registries would be offering preparations whose availability they cannot guarantee—without any medical justification whatsoever.

Offering such combined preparations would entail a non-medically indicated, probably life threatening, delay for the patient.

Naturally, such preparations are unacceptable for donor registries. For cord blood donations without a defined recipient, the rule therefore applies that donors have no legal claim on the cord blood, and that in the highly unlikely scenario of need, access can be made to the same conditions as for all other patients.

Recommendations for consulting doctors

Doctors who provide consultation and advice should pass the following recommendations to parents-to-be (according to [e13]):

- Parents-to-be should be advised to donate their newborn's umbilical cord blood if the opportunity exists. If a child requires a transplant, it is better to be able to use the blood of a healthy allogeneic donor.
- If parents already have a child with leukemia, it may be useful to donate the cord blood from the newborn for its ill sibling.
- Parents should be told that the probability of their child requiring its own cord blood is extremely low.
- Parents who in spite of this decide on storage for the child's own (autologous) use should not use loans or installments to pay for the storage; also they should gather detailed information about the companies that they are considering.

Acknowledgements

The authors thank all the hospitals for gynecology and obstetrics and their staff without which the José Carreras Cord Blood Bank would not exist. All cooperating hospitals are listed at www.stammzellbank.de. Our special thanks go to the colleagues at the José Carreras stem cell bank and the Netcord Office as well as José Carreras and the Jose Carreras Leukämie-Stiftung e.V. (the German José Carreras leukemia foundation, without whose financial support neither the successes in the transplantation of umbilical cord blood nor the implementation of the stem cell bank would have been possible to their current extent. The authors also thank the German Research Foundation (Deutsche Forschungsgemeinschaft), which enabled us to set up the research unit FOR 717.

Conflict of interest statement

Professor Gesine Kögler und Dr Verena Reimann work at the José-Carreras-Stammzellbank Düsseldorf (the public umbilical cord blood bank at Duesseldorf university hospital). Professor Dr Ursula Creutzig declares that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 4 August 2009, revised version accepted on 30 September 2009.

KEY MESSAGES

- Allogeneic hematopoietic stem cells from umbilical cord blood are already used successfully in the treatment of hematopoietic disorders.
- Autologous hematopoietic stem cells from cord blood are unsuitable for the treatment of hematopoietic disorders.
- Clinically relevant amounts of non-hematopoietic stem cells for potential use in regenerative medicine can be produced from only about 30% of all fresh (not previously cryopreserved) allogeneic cord blood donations.
- It is not possible to culture clinically relevant amounts of non-hematopoietic stem cells from cryopreserved cord blood donations.
- It remains to be seen whether umbilical cord blood banking for autologous use will be relevant in the future.

Translated from the original German by Dr Birte Twisselmann.

REFERENCES

1. Yamanaka S: A fresh look at iPS cells. *Cell* 2009; 137: 13–7.
2. Hanna J, Markoulaki S, Schorderet P, Carey BW, Beard C, Wernig M, et al.: Direct reprogramming of terminally differentiated mature B lymphocytes to pluripotency. *Cell* 2008; 133: 250–64.
3. Johnson FL: Placental blood transplantation and autologous banking—caveat emptor. *J Pediatr Hematol Oncol* 1997; 19: 183–6.
4. Kogler G, Tutschek B, Körschgen L, Platz A, Bender H, Wernet P: Die José Carreras Stammzellbank Düsseldorf im NET CORD/EURO-CORD-Verbund. *Gynäkologe* 2005; 38: 835–46.
5. Gluckman E, Broxmeyer HA, Auerbach AD, Friedman HS, Douglas GW, Devergie A, et al.: Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med* 1989; 321: 1174–8.
6. Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Scaradavou A, et al.: Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. *Lancet* 2007; 369: 1947–54.
7. Wagner JE, Laughlin M, Petz L: Seventh annual international umbilical cord blood transplantation symposium, Los Angeles, California, June 5–6, 2009. *Biol Blood Marrow Transplant* 2009.
8. Verneris MR, Brunstein CG, Barker J, Macmillan ML, Defor T, McKenna DH, et al.: Relapse risk after umbilical cord blood transplantation: enhanced graft versus leukemia effect in recipients of two units. *Blood* 2009.
9. Querol S, Mufti GJ, Marsh SG, Pagliuca A, Little AM, Shaw BE, et al.: Cord blood stem cells for hematopoietic stem cell transplantation in the UK: how big should the bank be? *Haematologica* 2009; 94: 536–41.
10. Kogler G, Sensken S, Airey JA, Trapp T, Muschen M, Feldhahn N, et al.: A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. *J Exp Med* 2004; 200: 123–35.
11. Kogler G, Sensken S, Wernet P: Comparative generation and characterization of pluripotent unrestricted somatic stem cells with mesenchymal stem cells from human cord blood. *Exp Hematol* 2006; 34: 1589–95.
12. Sensken S, Wacławczyk S, Knaupp AS, Trapp T, Enczmann J, Wernet P, et al.: In vitro differentiation of human cord blood-derived

- unrestricted somatic stem cells towards an endodermal pathway. *Cytotherapy* 2007; 9: 362–78.
13. Greschat S, Schira J, Kury P, Rosenbaum C, Souza Silva MA, Kogler G, et al.: Unrestricted somatic stem cells from human umbilical cord blood can be differentiated into neurons with a dopaminergic phenotype. *Stem Cells Dev* 2008; 17: 221–32.
 14. Buchheiser A, Liedtke S, Looijenga LH, Kogler G: Cord blood for tissue regeneration. *J Cell Biochem* 2009.
 15. Kogler G, Trapp T, Critser P, Yoder M: Future of cord blood for non oncology uses. *Bone Marrow Transplant* 2009; in press.
 16. Nishiyama N, Miyoshi S, Hida N, Uyama T, Okamoto K, Ikegami Y, et al.: The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. *Stem Cells* 2007; 25: 2017–24.
 17. Korf-Klingebiel M, Kempf T, Sauer T, Brinkmann E, Fischer P, Meyer GP, et al.: Bone marrow cells are a rich source of growth factors and cytokines: implications for cell therapy trials after myocardial infarction. *Eur Heart J* 2008; 29: 2851–8.
 18. Ghodsizad A, Niehaus M, Kogler G, Martin U, Wernet P, Bara C, et al.: Transplanted human cord blood-derived unrestricted somatic stem cells improve left-ventricular function and prevent left-ventricular dilation and scar formation after acute myocardial infarction. *Heart* 2009; 95: 27–35.
 19. Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Holschermann H, et al.: Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 2006; 355: 1210–21.
 20. Haverich A: Cardiac tissue engineering. *Eur J Cardiothorac Surg* 2008; 34: 227–8.
 21. Schmidt D, Mol A, Breyermann C, Achermann J, Odermatt B, Gossi M, et al.: Living autologous heart valves engineered from human prenatally harvested progenitors. *Circulation* 2006; 114(1Suppl): I125–31.
 22. Siepe M, Akhyari P, Lichtenberg A, Schlensak C, Beyersdorf F: Stem cells used for cardiovascular tissue engineering. *Eur J Cardiothorac Surg* 2008; 34: 242–7.
 23. Sodian R, Lueders C, Kraemer L, Kuebler W, Shakibaei M, Reichart B, et al.: Tissue engineering of autologous human heart valves using cryopreserved vascular umbilical cord cells. *Ann Thorac Surg* 2006; 81: 2207–16.
 24. Macchiarini P, Jungebluth P, Go T, Asnaghi MA, Rees LE, Cogan TA, et al.: Clinical transplantation of a tissue-engineered airway. *Lancet* 2008; 372: 2023–30.
 25. Haller MJ, Viener HL, Wasserfall C, Brusko T, Atkinson MA, Schatz DA: Autologous umbilical cord blood infusion for type 1 diabetes. *Exp Hematol* 2008; 36: 710–5.

Corresponding authors

Prof. Dr. rer. nat. Gesine Kögler
 Dr. rer. medic. Verena Reimann
 Universitätsklinikum Düsseldorf
 Institut für Transplantationsdiagnostik und Zelltherapeutika
 José Carreras Stammzellbank, Geb. 14.88
 Moorenstr. 5
 40225 Düsseldorf, Germany
 koegler@itz.uni-duesseldorf.de
 reimann@itz.uni-duesseldorf.de

For e-references please refer to:
www.aerzteblatt-international.de/ref5009

eTable available at:
www.aerzteblatt-international.de/article09m831

REVIEW ARTICLE

Stem Cells Derived From Cord Blood in Transplantation and Regenerative Medicine

Verena Reimann, Ursula Creutzig, Gesine Kögler

E-REFERENCES

- e1. Voltarelli JC, Couri CE, Stracieri AB, Oliveira MC, Moraes DA, Pieroni F, et al.: Autologous hematopoietic stem cell transplantation for type 1 diabetes. *Ann NY Acad Sci* 2008; 1150: 220–9.
- e2. Gitelman SE, Haller MJ, Schatz D: Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *JAMA* 2009; 302: 624–5.
- e3. Vendrame M, Cassady J, Newcomb J, Butler T, Pennypacker KR, Zigova T, et al.: Infusion of human umbilical cord blood cells in a rat model of stroke dose-dependently rescues behavioral deficits and reduces infarct volume. *Stroke* 2004; 35: 2390–5.
- e4. Garbuzova-Davis S, Sanberg CD, Kuzmin-Nichols N, Willing AE, Gemma C, Bickford PC, et al.: Human umbilical cord blood treatment in a mouse model of ALS: optimization of cell dose. *PLoS One* 2008; 3: e2494.
- e5. Ende N, Chen R: Parkinson's disease mice and human umbilical cord blood. *J Med* 2002; 33: 173–80.
- e6. Nikolic WV, Hou H, Town T, Zhu Y, Giunta B, Sanberg CD, et al.: Peripherally administered human umbilical cord blood cells reduce parenchymal and vascular beta-amyloid deposits in Alzheimer mice. *Stem Cells Dev* 2008; 17: 423–39.
- e7. Saporta S, Kim JJ, Willing AE, Fu ES, Davis CD, Sanberg PR: Human umbilical cord blood stem cells infusion in spinal cord injury: engraftment and beneficial influence on behavior. *J Hematother Stem Cell Res* 2003; 12: 271–8.
- e8. Moldenhauer A, Salama A: Stellenwert der Nabelschnurblutspende. *CME Praktische Fortbildung: Gynäkologie, Geburtsmedizin und Gynäkologische Endokrinologie* 2008; 1/2007: 26–44.
- e9. Platz A: Allogene und autologe Stammzelltransplantation aus Nabelschnurblut: öffentliche versus private Nabelschnurblutbanken. *Geburtsh Frauenheilk* 2008; 68: 291–3.
- e10. American Academy of Pediatrics. Work Group on Cord Blood Banking: Cord blood banking for potential future transplantation: subject review. *Pediatrics* 1999; 104(1 Pt 1): 116–8.
- e11. ACOG committee opinion number 399, February 2008: umbilical cord blood banking. *Obstet Gynecol* 2008; 111(2 Pt 1): 475–7.
- e12. Armson BA: Umbilical cord blood banking: implications for perinatal care providers. *J Obstet Gynaecol Can* 2005; 27: 263–90.
- e13. Ballen KK, Barker JN, Stewart SK, Greene MF, Lane TA: Collection and preservation of cord blood for personal use. *Biol Blood Marrow Transplant* 2008; 14: 356–63.
- e14. Stellungnahme der DAG-KBT zur Einlagerung von Nabelschnur-Restblut zur eigenen Verwendung Kryokonservierung und Langzeitlagerung von Nabelschnurstammzellen bei Neugeborenen zur späteren Eigennutzung. DAG-KBT 2002.
- e15. Stellungnahme der Sektion Transplantation und Zelltherapie der DGT (15. August 2005) zur Gewinnung und Langzeitlagerung von autologen und allogenen Stammzellpräparaten aus Nabelschnurblut: Indikationen und Grenzen. *Transfus Med Hemother* 2009; 32: 274–82.
- e16. Donner S, Winter A, Labude K: Stand der Forschung und der therapeutischen Anwendung von Nabelschnurblutstammzellen. Deutscher Bundestag 2009; Wissenschaftliche Dienste (WD 8 – 3000 172/08).
- e17. Edozien LC: NHS maternity units should not encourage commercial banking of umbilical cord blood. *BMJ* 2006; 333: 801–4.
- e18. Ethical aspects of umbilical cord blood banking. European Group on Ethics in Science and New Technologies. 2009.
- e19. Lubin BH, Shearer WT: Cord blood banking for potential future transplantation. *Pediatrics* 2007; 119: 165–70.
- e20. Commercial umbilical cord blood collection. RCM Midwives 2009; Guidance paper 1a(5).
- e21. Royal College of Obstetricians and Gynaecologists. Umbilical cord blood banking. London RCOG. 2009; SAC opinion paper 2 (revised).
- e22. WMDA policy statement on the utility of autologous or family cord blood unit storage. WMDA 2009 .
- e23. Mullighan CG, Flotho C, Downing JR: Genomic assessment of pediatric acute leukemia. *Cancer J* 2005; 11: 268–82.
- e24. Mullighan CG: Genomic analysis of acute leukemia. *Int J Lab Hematol* 2009; 31: 384–97.
- e25. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, et al.: Graft-versus-leukemia reactions after bone marrow transplantation. *Blood* 1990; 75: 555–62.
- e26. Gratwohl A, Baldomero H, Frauendorfer K, Rocha V, Apperley J, Niederwieser D: The EBMT activity survey 2006 on hematopoietic stem cell transplantation: focus on the use of cord blood products. *Bone Marrow Transplant* 2008; 41: 687–705.
- e27. Hayani A, Lampeter E, Viswanatha D, Morgan D, Salvi SN: First report of autologous cord blood transplantation in the treatment of a child with leukemia. *Pediatrics* 2007; 119: e296–e300.
- e28. Deutsche Standards für die nicht verwandte Blutstammzellspende. ZKRD (Zentrales Knochenmarkspender-Register Deutschland). 2007.
- e29. Vilmar K, Bachmann KD, Kurth R: Richtlinien zur Transplantation von Stammzellen aus Nabelschnurblut (C B = Cord Blood). *Dtsch Arztebl* 1999; 96(19): A 1297–304.
- e30. Zander AR, Bacher U, Finke J: Allogeneic stem cell transplantation in acute myeloid leukemia [Allogene Stammzelltransplantation bei der akuten myeloischen Leukämie]. *Dtsch Arztebl Int* 2008; 105(39): 663–9.
- e31. Haase A, Olmer R, Schwanke K, Wunderlich S, et al.: Generation of induced pluripotent stem cells from human cord blood. *Cell Stem Cell* 2009; 5: 434–41.

REVIEW ARTICLE

Stem Cells Derived From Cord Blood in Transplantation and Regener- ative Medicine

Verena Reimann, Ursula Creutzig,
Gesine Kögler

eTABLE

NETCORD members, inventory, and transplants, 1st quarter (March) 2009

CB Bank	Stored	Transplanted	Children	Adults
NETCORD/FACT accredited				
Sydney + Melbourne	16	522	261	261
Barcelona	11	497	201	279
Düsseldorf	15	582	277	278
Durham	19	918	288	638
France	6	926	12	11
Helsinki	2	23	56	80
Houston	7	136	50	73
Liège	2	123	130	121
London	10	251	196	181
Milan	7	377	1802	1104
New York	46	2906	39	54
Pavia	2	93	3312	3080
Subtotal	147	7354	261	261
not NETCORD/FACT accredited				
Athens	1314	6	5	5
Bratislava	277	1	0	1
Brisbane	3711	42	21	21
Florence	1102	64	31	33
Gauting	2477	53	21	32
Geneva	1578	42	1	45
Gothenburg	686	1	35	63
Liège	3642	80	66	62
Leuven	8470	129	35	19
Louvain	1900	97	9	64
Brussels	1335	28	35	48
Malaga	13 073	99	19	42
Mannheim	1733	67	85	34
Mexico City	1323	127	19	2
Padova	1393	53	2	12
Pescara	413	5	10	25
Prague	2947	22	27	21
Rome Lazio	1258	52	27	13
Santiago de Compostela	4997	49	10	8
Seoul	5755	23	10	684
Tel Hashomer	1463	18	230	1234
Tokyo	5555	914	698	4314
Subtotal	66 402	1972	4010	5
TOTAL	213 478	9326	5	1

Source: www.netcord.org/Archive/Charts/Inventory_March_09.gif