and neck in the randomized DAHANCA 6 and 7 study. *Radiother. Oncol.* **74**, 93–100 (2005).
88. Begg, A. C. *et al*. The value of pretreatment cell kinetic parameters as predictors for radiotherapy outcome in head and neck cancer: a multicenter analysis. *Radiother. Oncol.* **50**, 13–23 (1999).
89. Lee, C. M. *et al*. Correlation between human epidermal growth factor receptor family (EGFR, HER2, HER3, HER4), phosphorylated Akt (P-Akt), and clinical outcomes after radiation therapy in carcinoma of the cervix. *Gynecol. Oncol.* **99**, 415–421 (2005).
90. Eriksen, J. G. & Overgaard, J. Lack of prognostic and predictive value of CA IX in radiotherapy of squamous cell carcinoma of the head and neck with known modifiable hypoxia: an evaluation of the DAHANCA 5 study. *Radiother. Oncol.* **83**, 383–388 (2007).
91. Hemmati, H. D. *et al*. Cancerous stem cells can arise from pediatric brain tumors. *Proc. Natl Acad. Sci. USA* **100**, 15178–15183 (2003).
92. Bao, S. *et al*. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature* **444**, 756–760 (2006).
93. Bao, S. *et al*. Stem cell-like glioma cells promote tumor angiogenesis through vascular endothelial growth factor. *Cancer Res.* **66**, 7843–7848 (2006).
94. Rich, J. N. Cancer stem cells in radiation resistance. *Cancer Res.* **67**, 8980–8984 (2007).
95. Blazek, E. R., Foutch, J. L. & Maki, G. Daoy medulloblastoma cells that express CD133 are radioresistant relative to CD133- cells, and the $CD133^+$ sector is enlarged by hypoxia. *Int. J. Radiat. Oncol. Biol. Phys.* **67**, 1–5 (2007).
96. Phillips, T. M., McBride, W. H. & Pajonk, F. The response of $CD24^{-/low}/CD44^+$ breast cancer-initiating cells to radiation. *J. Natl Cancer Inst.* **98**, 1777–1785 (2006).
97. Woodward, W. A. *et al*. WNT/β-catenin mediates radiation resistance of mouse mammary progenitor cells. *Proc. Natl Acad. Sci. USA* **104**, 618–623 (2007).
98. Chen, M. S. *et al*. Wnt/ β-catenin mediates radiation resistance of $Sca1^+$ progenitors in an immortalized mammary gland cell line. *J. Cell Sci.* **120**, 468–477 (2007).
99. Tannock, I. F. & Lee, C. Evidence against apoptosis as a major mechanism for reproductive cell death following treatment of cell lines with anti-cancer drugs. *Br. J. Cancer* **84**, 100–105 (2001).
100. Brown, J. M. & Attardi, L. D. The role of apoptosis in cancer development and treatment response. *Nature Rev. Cancer* **5**, 231–237 (2005).
101. Hambardzumyan, D., Squatrito, M. & Holland, E. C. Radiation resistance and stem-like cells in brain tumors. *Cancer Cell* **10**, 454–456 (2006).
102. Ciampi, A., Kates, L., Buick, R., Kriukov, Y. & Till, J. E. Multi-type Galton–Watson process as a model for proliferating human tumour cell populations derived from stem cells: estimation of stem cell self-renewal probabilities in human ovarian carcinomas. *Cell Tissue Kinet.* **19**, 129–140 (1986).
103. Diehn, M. & Clarke, M. F. Cancer stem cells and radiotherapy: new insights into tumor radioresistance. *J. Natl Cancer Inst.* **98**, 1755–1757 (2006).
104. Wright, E. A. & Howard-Flanders, P. The influence of oxygen on the radiosensitivity of mammalian tissues. *Acta Radiologica* **48**, 26–32 (1957).
105. Gray, L. H., Conger, A. D., Ebert, M., Hornsay, S. & Scott, O. C. A. The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. *Br. J. Radiol.* **26**, 638–648 (1953).
106. Vaupel, P. & Mayer, A. Hypoxia in cancer: significance and impact on clinical outcome. *Cancer Metastasis Rev.* **26**, 225–239 (2007).
107. Overgaard, J. Hypoxic radiosensitization: adored and ignored. *J. Clin. Oncol.* **25**, 4066–4074 (2007).
108. Hu, C. J., Wang, L. Y., Chodosh, L. A., Keith, B. & Simon, M. C. Differential roles of hypoxia-inducible factor 1α (HIF-1α) and HIF-2α in hypoxic gene regulation. *Mol. Cell. Biol.* **23**, 9361–9374 (2003).
109. Covello, K. L. *et al*. HIF-2α regulates Oct-4: effects of hypoxia on stem cell function, embryonic development, and tumor growth. *Genes Dev.* **20**, 557–570 (2006).
110. Gordan, J. D., Bertout, J. A., Hu, C. J., Diehl, J. A. & Simon, M. C. HIF-2α promotes hypoxic cell proliferation by enhancing c-myc transcriptional activity. *Cancer Cell* **11**, 335–347 (2007).
111. Gustafsson, M. V. *et al*. Hypoxia requires notch signaling to maintain the undifferentiated cell state. *Dev. Cell* **9**, 617–628 (2005).
112. Platet, N. *et al*. Influence of oxygen tension on CD133 phenotype in human glioma cell cultures. *Cancer Lett.* **258**, 286–290 (2007).
113. Quennet, V. *et al*. Tumor lactate content predicts for response to fractionated irradiation of human squamous cell carcinomas in nude mice. *Radiother. Oncol.* **81**, 130–135 (2006).
114. Ling, C. C. *et al*. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. *Int. J. Radiat. Oncol. Biol. Phys.* **47**, 551–560 (2000).
115. Cordes, N., Seidler, J., Durzok, R., Geinitz, H. & Brakebusch, C. β1-integrin-mediated signaling essentially contributes to cell survival after radiation-induced genotoxic injury. *Oncogene* **25**, 1378–1390 (2006).
116. Moore, K. A. & Lemischka, I. R. Stem cells and their niches. *Science* **311**, 1880–1885 (2006).
117. Scadden, D. T. The stem-cell niche as an entity of action. *Nature* **441**, 1075–1079 (2006).
118. Gilbertson, R. J. & Rich, J. N. Making a tumour's bed: glioblastoma stem cells and the vascular niche. *Nature Rev. Cancer* **7**, 733–736 (2007).
119. Hambardzumyan, D. *et al*. PI3K pathway regulates survival of cancer stem cells residing in the perivascular niche following radiation in medulloblastoma *in vivo*. *Genes Dev.* **22**, 436–48 (2008).
120. Bonner, J. A. *et al*. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N. Engl. J. Med.* **354**, 567–578 (2006).
121. Pignon, J. P., Bourhis, J., Domenge, C. & Designe, L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* **355**, 949–955 (2000).
122. Krause, M. *et al*. EGFR-TK inhibition before radiotherapy reduces tumour volume but does not improve local control: Differential response of cancer stem cells and nontumourigenic cells? *Radiother. Oncol.* **83**, 316–325 (2007).
123. Baumann, M. *et al*. Selective inhibition of the epidermal growth factor tyrosine kinase by BIBX1382BS improves growth delay but not local control after fractionated irradiation in human FaDu squamous cell carcinoma in nude mice. *Int. J. Radiat. Biol.* **79**, 1547–559 (2003).
124. Zips, D. *et al*. Experimental study on different combination schedules of VEGF-receptor inhibitor PTK787/ZK222584 and fractionated irradiation. *Anticancer Res.* **23**, 3869–3876 (2003).
125. Zips, D. *et al*. Impact of adjuvant inhibition of vascular endothelial growth factor receptor tyrosine kinases on tumor growth delay and local tumor control after fractionated irradiation in human squamous cell carcinomas in nude mice. *Int. J. Radiat. Oncol. Biol. Phys.* **61**, 908–914 (2005).
126. Weppler, S. A. *et al*. Response of U87 glioma xenografts treated with concurrent rapamycin and fractionated radiotherapy: Possible role for thrombosis. *Radiother. Oncol.* **82**, 96–104 (2007).
127. Milas, L. *et al*. *In vivo* enhancement of tumor radioresponse by C225 antiepidermal growth factor receptor antibody. *Clin. Cancer Res.* **6**, 701–708 (2000).
128. Nasu, S., Ang, K. K., Fan, Z. & Milas, L. C225 antiepidermal growth factor receptor antibody enhances tumor radiocurability. *Int. J. Radiat. Oncol. Biol. Phys.* **51**, 474–477 (2001).
129. Krause, M. *et al*. Different classes of EGFR inhibitors may have different potential to improve local tumour control after fractionated irradiation: a study on C225 in FaDu hSCC. *Radiother. Oncol.* **74**, 109–115 (2005).
130. Kozin, S. V. *et al*. Vascular endothelial growth factor receptor-2-blocking antibody potentiates radiation-induced long-term control of human tumor xenografts. *Cancer Res.* **61**, 39–44 (2001).
131. Bayer, C. *et al*. PAI-1 levels predict response to fractionated irradiation in 10 human squamous cell carcinoma lines of the head and neck. *Radiother. Oncol.* **86**, 361–368 (2008).
132. Schutze, C. *et al*. Effect of increase of radiation dose on local control relates to pre-treatment FDG uptake in FaDu tumours in nude mice. *Radiother. Oncol.* **83**, 311–315 (2007).
133. Suit, H. D., Sedlacek, R. & Thames, H. D. in *Rodent tumor models in experimental cancer therapy* (ed. Kallman, R. F.) 138–148 (Pergamon Press, New York, 1987).

Acknowledgement:
This work was supported in part by the Deutsche Forschungsgemeinschaft (Ba 1433) and by the National Cancer Institute of Canada with funds raised by the Tery Fox Run (15004). The authors wish to thank H.D. Thames, Houston, Texas, USA for helpful discussions.

DATABASES
Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
β-catenin | CD24 | CD44 | EGFR | EPAS1 | H2AX | HIF1α | FRAP1 | MYC | NOTCH1 | p53 | POU5F1 | PROM1
National Cancer Institute: http://www.cancer.gov/
breast cancer | chronic myeloid leukaemia | glioblastoma

FURTHER INFORMATION
M. Baumann's homepage: http://www.oncoray.de

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

SCIENCE AND SOCIETY

Banking on cord blood stem cells

Michael J. Sullivan

Abstract | Umbilical cord blood gifted to non-profit public cord blood banks is now routinely used as an alternative source of haematopoietic stem cells for allogeneic transplantation for children and adults with cancer, bone marrow failure syndromes, haemoglobinopathies and many genetic metabolic disorders. Because of the success and outcomes of public cord banking, many companies now provide private cord banking services. However, in the absence of any published transplant evidence to support autologous and non-directed family banking, commercial cord banks currently offer a superfluous service.

The altruistic gifting of umbilical cord blood stem cells from one's newborn child for the benefit an anonymous individual anywhere across the world is a remarkably generous gesture. These unrelated (allogeneic; for a glossary of terms used in this article, see BOX 1) cord blood donations are stored and curated by an international network of 36 public non-profit umbilical cord blood banks in 23 countries, and made available to accredited stem cell transplant centres for the treatment of life-threatening diseases, including cancer, bone marrow failure syndromes and genetic metabolic

disorders (TABLE 1). The first banking of unrelated umbilical cord blood began in New York in 1993, and similar public cord banks were established soon after in Paris, Milan, Dusseldorf and Sydney[1–3]. By the end of 2007, Bone Marrow Donors Worldwide (see URL in Further information) recorded over 280,000 stored cord blood units available for unrelated stem cell transplantation and in 2007 the Eurocord network (see URL in Further information) published the outcome of over 3,000 unrelated cord blood transplants. In addition to unrelated cord blood banking, most accredited stem cell transplant centres offer directed cord blood banking from the siblings of patients who might need a future stem cell transplant, for instance children with high-risk acute leukaemias who might benefit from an allogeneic stem cell transplant should their disease relapse.

Not long after the establishment of public non-profit cord blood banks, several private, for-profit providers in the USA began offering expectant parents a service to store their newborn child's umbilical cord blood for possible autologous or related (family) allogeneic stem cell transplantation, or future stem cell therapy[4]. Fifteen years later, there are nearly 150 private umbilical cord blood banks listed worldwide on the 'Parent's Guide to Cord Blood' website (see URL in Further information), most notably in the USA, Europe, and Central and South America, and more recently Australia, New Zealand, the Middle East, India, and other parts of Asia.

The establishment of commercial cord blood banks was controversial at the time and remains so because clinical evidence supporting autologous cord blood storage was, and still is, lacking[5–9]. Indeed, in its 2004 report on the ethics of umbilical cord blood banking, the European Union Group on the Ethics of Science and New Technologies raised serious ethical concerns regarding commercial cord blood banking (BOX 2). The principal ethical objection is to the promotion to expectant parents of the future benefits of autologous cord banking as a biological insurance to treat diseases for which at present there is "no medical evidence for the validity of treatment"[10].

The published evidence supporting unrelated allogeneic cord blood transplantation for the treatment of both children and adults with cancer is compelling, and cord blood transplants are now a routine clinical procedure[11–21]. Given this, why are there persisting medical and ethical concerns regarding commercial autologous cord blood banking[7,22–28]? Moreover, what, if any, scientific or clinical evidence exists to support storing cord blood for either autologous cord transplantation, or future stem cell-based therapy?

Public umbilical cord blood banks

The inheritance of the human leukocyte antigen (HLA) tissue antigens means the chance of any sibling being a full tissue match for an allogeneic bone marrow transplant is 25% and, given the small size of modern families, the chance of finding a related fully matched donor is only about 30%. For the remaining 70% of patients, an unrelated donor stem cell source must be found. HLA haplotypes are highly polymorphic and even with 11 million tissue-typed donors registered on international bone marrow donor registries, finding a full match for patients in many ethnic groups, especially those of mixed race, remains a challenge. Many tissue types are often underrepresented in bone marrow donor registries, or patients might have rare or restricted tissue types[29]. Indeed, although a matched unrelated donor can be found for up to 75% of patients of Western European origin, for many ethnic groups the reverse is true with no more than 20–30% being matched, leaving a substantial proportion of patients with neither a related sibling donor nor an unrelated bone marrow donor[3,29]. Public cord blood banks were established essentially to overcome this problem. Umbilical cord blood is more permissive of donor–host tissue mismatch, allowing a greater number of patients to benefit from a smaller donor pool. In addition, banked umbilical cord blood has several other advantages over bone marrow registry donors: stored cord blood is already tissue-typed, is free of viral infection, has a known cell count and is immediately available for transplant[30]. Since the first umbilical cord transplant in 1988 (REFS 2,31) (BOX 3), over 6,000 cord blood stem cell transplants have been recorded by Netcord (see URL in Further information).

Box 1 | **Glossary of terms used in this article**

Allogeneic haematopoietic stem cell transplantation
Stem cells are collected from a related or unrelated donor, and transplanted into the patient following myeloablative conditioning chemotherapy or chemoradiotherapy to reconstitute the bone marrow and provide a graft-versus-leukaemia or graft-versus-tumour effect.

Autologous haematopoietic stem cell transplant
Haematopoietic stem cells are collected from the patient before treatment, and re-infused following myeloablative conditioning chemotherapy or chemoradiotherapy to reconstitute the bone marrow.

Graft-versus-host disease
A donor-derived T-cell-mediated immune response against host tissue following allogeneic haematopoietic stem cell transplantation. May be acute or chronic and occurs in several grades of severity most commonly associated with a skin rash, liver dysfunction, gastrointestinal symptoms and lung disease.

Graft versus leukaemia
A donor-derived immunological response against residual malignancy in the host following allogeneic haematopoietic stem cell transplantation.

Human leukocyte antigens (HLA)
Conventional HLA tissue typing classifies antigens into HLA class I (HLA-A and HLA-C) and class II (HLA-DR). Individuals have three pairs of HLA-A, B and DR antigens and a full tissue match by conventional typing is termed a 6/6 match. Class II HLA DR antigens are highly polymorphic and are typed and subtyped by molecular methods.

Induced pluripotent stem cells
Recently developed primitive stem cell lines derived from mature differentiated tissue by the retroviral transfer of a panel of developmentally regulated genes. Capable of differentiation into multiple cell lineages.

Myeloablative
Describes chemotherapy or chemoradiotherapy given before transplantation to treat the malignancy that ablates the patient's bone marrow.

Multipotent stem cells
A committed stem cell with a restricted differentiation capacity. Haematopoietic stem cells are tissue-specific multipotent stem cells that are able to differentiate into multiple haematopoietic cell lineages, erythroid, myeloid and lymphoid cells, but not other tissues.

Pluripotent stem cells
A primitive stem cell capable of differentiation into multiple tissue types and multiple cell lineages.

Table 1 | **Indications for haematopoietic stem cell transplantation**

Disease	AlloSCT	AlloCB	AutoSCT	AutoCB	Comment
Leukaemia and lymphoma					
ALL; standard and high-risk	N	N	N	N	
ALL; very high-risk and relapse	Y	Y	N	N	Clinical trial-based therapy. AutoCB not indicated
AML; standard-risk	N	N	N	N	
AML; high-risk and relapse	Y	Y	N	N	Clinical trial-based therapy. AutoCB not indicated
AML; secondary (treatment-related)	Y	Y	N	N	
JMML	Y	Y	N	N	
CML; standard-risk	N	N	N	N	
CML; relapsed	Y	Y	N	N	
CLL	Y	Y	N	N	
HD; low stages, localized relapse	N	N	N	N	
HD; advanced-stage, relapse	Y	Y	Y	N/Y	AutoSCT indicated, no advantage for autoCB
NHL; (B and T cell) all stages	N	N	N	N	
NHL; relapsed	Y	Y	Y	N/Y	AlloSCT and autoSCT indicated, no advantage for autoCB
Myeloproliferative disorders					
MDS and refractory anaemia	Y	Y	N	N	
Other myeloproliferative disorders	Y	Y	N	N	
Multiple myeloma	Y	Y	Y	N/Y	AlloSCT and autoSCT indicated, no advantage to autoCB
Lymphohistiocytic disorders					
LCH, standard-risk	N	N	N	N	
LCH, relapsed	Y	Y	N	N	
HLH	Y	Y	N	N	
Bone marrow failure					
Aplastic anaemia, congenital	Y	Y	N	N	
Aplastic anaemia, mild, moderate	N	N	N	N	Immunotherapy more effective than SCT
Aplastic anaemia, severe	Y	Y	N	N/Y	AutoCB indicated in the absence of alloSCT or alloCB donor
Fanconi anaemia	Y	Y	N	N	
Congenital anaemias	Y	Y	N	N	
Childhood solid tumours					
Ewing sarcoma	N	N	Y	N	AutoSCT only in clinical trials
Medulloblastoma, standard-risk	N	N	N	N	
Medulloblastoma, high-risk	N	N	Y	N	AutoSCT only in clinical trials
Neuroblastoma, stage 1–2	N	N	N	N	
Neuroblastoma, stage 3–4	N	N	Y	Y	See text, no advantage for autoCB compared with autoSCT
Rhabdomyosarcoma	N	N	N	N	SCT not effective for advanced-stage disease
Wilms tumour	N	N	N	N	AutoSCT for rare high-risk and relapsed disease only
Hepatoblastoma	N	N	N	N	AutoSCT for rare high-risk and relapsed disease only
Retinoblastoma	N	N	N	N	AutoSCT for high-risk relapsed disease only
Adult solid tumours					
Breast cancer, stage 1–3	N	N	N	N	
Breast cancer, advanced-stage	N	N	Y	N	AutoSCT in clinical trials only, see text
RCC low-stage	N	N	N	N	
RCC advanced-stage	N	N	Y	N	AutoSCT only in clinical trials, see text
Testicular cancer	N	N	Y	N	AutoSCT only in clinical trials
Other					
Genetic metabolic disorders	Y	Y	N	N	AlloSCT and AlloCB only
Haemoglobinopathies	Y	Y	N	N	
Immune deficiency syndromes	Y	Y	N	N	

Haemoglobinopathies include sickle cell disease and thalassaemia. Immune deficiencies include chronic granulomatous disease, severe combined immunodeficiency, Chediak–Higashi syndrome, lymphoproliferative disorders and Kostmann syndrome. Other myeloproliferative disorders include myelofibrosis, polycythemia vera and essential thrombocythaemia. ALL, acute lymphoblastic leukaemia; alloCB, allogeneic cord blood stem cell transplantation; alloSCT, related and unrelated allogeneic bone marrow, peripheral blood; AML, acute myeloid leukaemia; autoCB, autologous cord blood transplantation; autoSCT, autologous bone marrow and peripheral blood stem cell transplantation; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; HD, Hodgkin disease; HLH, haemophagiocytic lymphohistiocytosis; LCH, Langerhans cell histiocytosis; JMML, juvenile myelomonocytic leukaemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; RCC, renal cell carcinoma.

There are now 36 international public cord banks that are members of the NetCord consortium, providing access to unrelated cord blood donations for over 500 affiliated international transplant centres. Leading US transplant advocates recently succeeded in gaining funding for an expanded national public cord banking programme coordinated by the National Marrow Donor Program, with a target of 150,000 banked cords aimed at overcoming the problem of tissue matching for ethnic groups but with sufficient cords to lessen the risk of major tissue mismatch-related graft-versus-host disease (GVHD)[3].

Private commercial cord banks

Private cord blood banking is now available in most parts of the world with some notable exceptions, such as Italy and Spain, where private cord banking is not permitted. Private banks offer expectant parents the opportunity to store their newborn child's cord blood for future treatment of cancer and genetic diseases, and for possible future stem cell therapy (BOX 4). For a variable fee, depending on country (between $1,000–2,500 in the USA, for example), parents can bank their child's umbilical cord blood for autologous use, or for a family member. Notably though, New Zealand and Australia restrict the use of privately collected cord blood to the individual child, and prohibit use by a sibling or relative[28]. Commercial banks rely on the local health-care provider, the doctor or midwife, to collect the cord blood at birth and forward it to the bank for long-term storage. Although this may be convenient for the purposes of collection, it introduces the potential for poor-quality or low-yield cord collections[32].

A systematic review of the information on the English language websites of 148 commercial cord blood banks reveals a pattern of confusing and potentially misleading information regarding the benefits of autologous and family cord blood storage. Private cord banks all publish remarkably similar lists of diseases that "can be treated" by umbilical cord blood transplants, including cancer, bone marrow failure syndromes and genetic disorders (see Parents Guide to Cord Blood URL in Further information). Most of these are diseases treatable only with an allogeneic cord blood transplant (related or unrelated), but many commercial banks do not explain the difference between autologous and allogeneic cord transplantation clearly enough, leaving the potential customer to assume that the indications for related and unrelated allogeneic transplantation also apply to autologous transplants, which they do not. Most commercial banks also list many conditions that might be treated in the future by as yet undeveloped stem cell therapies for regenerative medicine (BOX 4). A notable exception is the recently established UK-based 'Branson Bank' (Virgin Health Bank), a unique hybrid commercial bank offering public and private banking of cord blood units. The information regarding the potential future benefits is refreshingly accurate and clear[33].

With both private and public cord banks now well-established, what are the scientifically proven advantages of using cord blood for haematopoietic stem cell transplantation and is there any basis to claims that umbilical cord blood-derived stem cells offer a unique opportunity for future regenerative medicine?

Box 2 | **Opinions regarding commercial autologous cord blood banking**

European Commission's Group on Ethics in Science and New Technologies (EGE) report on the ethics of private umbilical cord banking[10]

"The legitimacy of commercial cord blood banks for autologous use should be questioned as they sell a service, which has presently, no real use regarding therapeutic options. Thus they promise more than they can deliver. The activities of such banks raise serious ethical criticisms."

"If commercial banks are allowed (in any EU member state), appropriate information should be given to consumers willing to use their services, including the fact that the likelihood that samples may be used to treat one's child is currently negligible, that future therapeutic possibilities are of a very hypothetical nature, and that up until now there is no indication that the present research will lead to specific therapeutic applications on one's own cord blood cells."

"… information should be particularly explicit, that the auto conservation has little value in the current state of scientific knowledge. This information should be made clear on all media, including Internet, and in any contracts linking commercial banks to their customers."

American Academy of Pediatrics[9,22]

"Cord blood donation should be discouraged when cord blood stored in a bank is to be directed for later personal or family use, because most conditions that might be helped by cord blood stem cells already exist in the infant's cord blood (ie, premalignant changes in stem cells). Physicians should be aware of the unsubstantiated claims of private cord blood banks that promise to insure infants or family members against serious illnesses in the future by use of the stem cells contained in cord blood".

"Given the difficulty of making an accurate estimate of the need for autologous transplantation and the ready availability of allogeneic transplantation, private storage of cord blood, as biological insurance, is unwise."

Royal College of Obstetricians and Gynaecologists (RCOG)[10]

"The RCOG strongly supports the concept of a NHS Cord Blood Bank for allogeneic storage of donated cord blood and would like to see it well funded. However, it remains unconvinced of the benefit of personal commercial banking for low-risk families."

World Marrow Donor Association: Policy Statement for the Utility of Autologous or Family Cord Blood Unit Storage (see URL in further information)

"Today the likelihood that an autologous cord blood unit will be used for transplantation is very low. There is currently no clear proof that these cells will be able to be used for regenerative medicine or to treat other diseases in the future."

"Where autologous cord blood banks are being established, the promotional material or information provided to families must be accurate, and fully informed consent to cord blood storage must be obtained".

"The legitimacy of commercial cord blood banks for autologous use should be questioned as they sell a service which has presently no real use regarding therapeutic options. Thus they promise more than they can deliver."

Umbilical cord blood-derived stem cells

In the last weeks of pregnancy, the human fetus greatly expands haematopoiesis in preparation for its physiological transition at birth. The newborn circulation, the placenta and umbilical cord at birth are rich with haematopoietic stem cells, a type of multipotent stem cell with the capacity to differentiate into the three classes of blood cell: erythroid, myeloid and lymphoid. However, unlike embryonic stem cells, umbilical cord blood stem cells are not pluripotent, and are biologically similar to their adult counterparts. Umbilical cord blood differs in two crucial ways, making it especially suited as a source for haematopoietic stem cell transplantation.

First, cord blood-derived lymphocytes are immunologically naive: they have an unmodified T-cell repertoire, the T cells

Box 3 | **Non-malignant diseases treated with cord blood transplantation**

The first reported umbilical cord transplant in 1988 was a matched sibling transplant for the treatment of a child with Fanconi anaemia, a complex autosomal recessive disorder that is associated with bone marrow failure[31]. More recently, pre-implantation genetic diagnosis has been applied to the selection of a matched sibling donor for cord blood transplantation in Fanconi anaemia, so-called 'saviour siblings'[92]. Related and unrelated cord blood transplants remain an option for treatment of patients with Fanconi anaemia whose prognosis without an allogeneic transplant remains poor. Similarly, unrelated cord blood transplantation is an option for the treatment of patients with haemoglobinopathies, genetic metabolic disorders and bone marrow failure syndromes, and those with severe acquired aplastic anaemia who do not have a related donor and who fail immune-based therapy[36,37,87,93–95].

produce fewer activating cytokines, and they have fewer natural killer (NK) cells[34]. On allogeneic transplantation, cord blood haematopoietic stem cells produce an attenuated donor-derived immune response, and when compared with unrelated bone marrow-derived stem cells, cause significantly less acute and chronic GVHD[19,35–36]. Less severe GVHD permits less stringent HLA tissue matching and a greater degree of tissue mismatch of cord blood compared with bone marrow-derived haematopoietic stem cells[1,3].

Second, cord blood stem cells have a higher proliferative potential than bone marrow, meaning significantly fewer cells are required to recapitulate haematopoiesis[1–3,36]. Approximately 50–100 ml of umbilical cord blood harvested at birth has sufficient haematopoietic stem cells for transplant to a child or small adult and, with improved methods of harvesting and storage, umbilical cord blood units are now routinely used for adult stem cell transplants[37].

Human umbilical cord blood also contains other non-haematopoietic stem cells, most notably mesenchymal stem cells, another class of multipotent stem cell that is capable of differentiating into multiple lineages of structural and supporting tissues such a muscle, bone and other soft tissues[38]. However, this class of cell is not unique; they are biologically similar to adult multipotent stem cells but, unlike adult bone marrow, are present in only low numbers in the cord and do not have the pluripotency of primitive embryonic stem cells[39,40].

Undoubtedly, cord blood-derived haematopoietic and non-haematopoietic stem cells differ from their adult counterparts by having undergone fewer total cell divisions and, being 'biologically younger', they have been subject to less genotoxic damage and epigenetic modification.

Haematopoietic stem cell transplants

Allogeneic and autologous stem cell transplants are distinctly different procedures with different clinical indications, clinical course and outcomes (TABLE 1).

Autologous stem cell transplants harvest the patient's own haematopoietic stem cells, either directly from the bone marrow or by apheresis of the peripheral blood; these haematopoietic stem cells are later re-infused into the patient following myeloablative conditioning chemotherapy or chemoradiotherapy. Autologous stem cell transplants do not in themselves treat the underlying disease process; it is the conditioning therapy that is curative. Re-infusion of autologous stem cells rescues the haematopoiesis destroyed by the myeloablative therapy, permitting more intense or higher-dose therapy to be delivered.

Autologous transplants are used in cases where the underlying disease process does not involve the bone marrow (with the exception of advanced-stage neuroblastoma, see below), in particular as consolidation treatment for some childhood and adult solid tumours, for salvage treatment of various relapsed lymphomas (although an allogeneic transplant may be preferred), and for treatment of progressive multiple myeloma (see the American Society for Blood and Marrow Transplantation URL in Further information). However, autologous transplants have a limited role in the treatment of diseases involving the bone marrow itself and currently have no role in the treatment of acute or chronic leukaemias, or bone marrow failure syndromes, and are of no benefit in the treatment of genetic and metabolic disorders[41]. Although autologously derived cells will be the cell source for gene therapy of cancer and genetic disorders, autologous cord blood stem cells appear to have no special advantage over similar stem cells of adult origin.

Allogeneic transplants use healthy donor haematopoietic stem cells from an unaffected tissue-matched relative, most often a sibling, or an anonymous matched unrelated donor (MUD) from an international bone marrow donor registry or public umbilical cord bank. Directed cord blood banking from siblings is a valuable source of stem cells for allogeneic transplantation for patients with a known life-threatening disease that may benefit from a future haematopoietic stem cell transplant. Although the total number of directed cord blood samples stored is unknown, it is small by comparison with both unrelated public banking and autologous private banking.

Haematopoietic stem cells are harvested directly from the donor bone marrow or peripheral blood immediately before transplant, or in the case of cord blood the stem cells are harvested from the umbilical cord of sibling or an anonymous donor and cryopreserved at birth[2]. The cells are infused into the patient following myeloablative chemotherapy or chemoradiotherapy.

Allogeneic transplants are indicated in the treatment of high-risk acute and chronic leukaemias, bone marrow failure syndromes such as severe aplastic anaemia, and relapsed leukaemia and lymphoma. They benefit specific genetic metabolic disorders in which transplantation of an unaffected bone marrow would ameliorate or cure the condition[42–45].

When patients with acute leukaemia are treated with the same conditioning therapy, those undergoing allogeneic transplants have significantly better outcomes compared with autologous transplants, but this is not simply due to the absence of disease in the donor marrow[46]. On engraftment, donor-derived T cells initiate a graft versus leukaemia (GVL) immune response directed at residual malignancy with a significant overall survival benefit[47]. A similar immune-mediated graft-versus-tumour effect is also evident in lymphoma and might account for an added survival benefit seen with allogeneic transplants in some adult solid tumours, such as advanced-stage breast cancer[41,47,48].

However, GVHD is a major cause of transplant-related morbidity and mortality following matched related and unrelated allogeneic transplants, the risk and severity of which is directly related to the source of haematopoietic stem cells and closeness of HLA tissue matching. Matched sibling donor transplants are generally associated with less severe GVHD compared with matched unrelated and mismatched donor transplants[3,41], whereas peripheral blood-derived haematopoietic stem cells cause more severe GVHD compared with bone marrow and cord blood stem cells.

Outcome of cord stem cell transplants

Allogeneic transplants. By far the majority of cord blood stem cell transplants are sourced from anonymous, unrelated donors through public umbilical cord banks. Unrelated cord blood transplants now account for over 20% of all stem cell transplants (50% in Japan), and since 2005 more cord transplants have been done in adults than in children[36]. The most recent Eurocord report (see URL in Further information) from 1988–2007 records the outcome of some 3,372 umbilical cord transplants, done in 43 countries at 373 transplant centres. Of these, 2,965 were unrelated donor transplants, 359 were related donors but only three were autologous.

Data from Eurocord, multiple disease-specific reports and a recent meta-analysis show that the long-term survival after cord blood transplantation in both children and adults is now comparable to bone marrow transplantation, supporting the wider use of cord blood banking and transplantation[11–21,49]. A recent large study of cord blood transplantation in children with high-risk and relapsed acute leukaemia reported a 5-year leukaemia-free survival for matched, unrelated cord blood transplantation similar to that of matched bone marrow transplantation[13]. Moreover, this study made a crucially important observation: patients transplanted with one- and two-allele-mismatched cord blood samples have transplant-related mortality and leukaemia-free outcomes that are comparable to fully matched unrelated bone marrow donors, but only for transplants using cords with a high cell count. This is a compelling result, as it supports the notion that mismatched transplants from unrelated cord blood banks can make stem cell transplantation available to those groups currently underrepresented by the large bone marrow registries. However, it also provides clear evidence that successful cord blood transplantation depends on the volume and quality of the collected cord blood unit[13]. Netcord and the Foundation for Cellular Therapies (FACT; see URLs in Further information) have recently developed joint standards for cord blood banking (JACIE guidelines, see URL in further information), including standard operating procedures and quality control guidelines for the collection, storage, assay and curating of cord blood units.

Autologous cord blood transplantation for cancer. Over the last 15 years there have been only three published single-case reports of autologous cord stem cell transplants using cord blood sourced from commercial umbilical cord banks[50–52]. With so many umbilical cord blood units in commercial banks, it is indeed surprising that no commercial provider has ever published peer-reviewed data on the number of cord blood units stored, the number of units used and the outcome of any autologous transplants.

Most commercial cord bank websites contain testimonial cases, with the majority of these being the result of directed cord storage of siblings for the transplant of patients with known high-risk diseases. Although this form of directed cord banking for transplantation is a recommended and standard procedure as a future source of haematopoietic stem cells, such directed cord blood donations can also be collected, processed and stored at no cost to the patient by local blood services associated with transplant centres. Moreover, a fully matched sibling can donate bone marrow at any time in the future should it become necessary.

The first reported case of an autologous cord transplant from a commercial cord bank was an infant with a stage 4 neuroblastoma, an aggressive solid tumour of early childhood that can metastasize to bones and bone marrow[50]. Advocates of private banking frequently cite neuroblastoma as justification for autologous cord blood collection. However, neuroblastoma is a complex cancer, with many clinical and biological subtypes, each managed differently, and autologous transplants are indicated in only 50% of cases. Furthermore, in most cases an autologous bone marrow harvest, or more preferably a peripheral blood stem cell harvest, is possible following an initial course of treatment, so the only absolute indication for an autologous cord transplant would be cases of neuroblastoma with bone marrow involvement at diagnosis that failed to clear with conventional chemotherapy[53]. However, failure to clear bone marrow neuroblastoma with induction chemotherapy signifies chemotherapy-resistant neuroblastoma, which has a poor prognosis and is unlikely to be cured with an autologous transplant[54,55]. More recently, tandem bone marrow autologous transplants have been associated with an improved outcome for advanced-stage neuroblastoma, and are now the subject of open clinical trials[53,56]. Tandem autologous transplants would not be possible from a single autologous cord blood stem cell harvest. Thus the available data does not justify autologous cord blood storage for the future treatment of neuroblastoma in childhood.

Most commercial umbilical cord banks also list several other solid tumours as treatable by autologous transplantation. However, contrary to the marketing, autologous transplants are not in routine

Box 4 | **Is cord banking an insurance for future stem cell medicine?**

Although it might appear far-sighted and progressive to bank one's umbilical cord for future stem cell therapy, does the available evidence justify this, and are umbilical cord stem cells really unique when compared with other multipotent stem cells?

The prospect of stem cell therapy is tantalizingly close, although reviewing the publicity material on many commercial cord blood bank websites would give the lay public the impression that stem cell therapy for regenerative medicine is already in routine clinical use — it is not!

Stem cell therapies aim to derive patient-specific differentiated tissues to repair tissue or organs damaged by degenerative diseases. These new tissues or organs will be derived *in vitro* by the controlled differentiation of pluripotent stem cells. However, the source of these stem cells has been controversial, especially the prospect of using embryonic stem cell lines to induce pluripotency from differentiated somatic cells using nuclear transfer technology[96,97].

Ongoing ethical and scientific concerns around embryonic stem cell-based therapies has driven the recent development of methods for the induction of pluripotent stem cells from existing adult stem cells or from differentiated tissues. Several recent studies have reported the successful induction of pluripotency from differentiated tissues such as skin fibroblasts by the retroviral expression of a panel of developmentally regulated genes[98–101]. These reprogrammed somatic tissues have the developmental capacity of pluripotent stem cells, and genetic and epigenetic analysis shows that induced pluripotent stem cells (iPSs) are indistinguishable from pluripotent embryonic stem cells[98,100,101].

The therapeutic potential of iPSs was recently been demonstrated in a mouse sickle cell anaemia model[101]. Although many technical issues remain, particularly the use of retroviral transforming genes to induce pluripotency, this proof-of-principle research is of crucial importance in regard to the future of stem cell-based therapies. The induction of patient-specific pluripotent cells derived from mature tissue will inevitably replace need for an embryonic stem cell-based approach, and will obviate any need or justification for autologous cord blood banking.

clinical use for the upfront treatment of Wilms tumour, rhabdomyosarcoma, osteosarcoma or other sarcomas. They are used as part of clinical trial-based treatment for Ewing sarcoma with isolated pulmonary metastases, relapsed high-grade non-Hodgkin lymphoma and as experimental therapy in some brain tumours[57–65] (TABLE 1). However, in all these diseases, bone marrow involvement is rare and an autologous bone marrow or peripheral blood stem cell harvest can be done following initial diagnosis, precluding the need for autologous cord blood storage. Autologous transplantation is used as salvage therapy for relapsed Wilms tumour, in which marrow involvement is rare[66], but has little or no role in the treatment of metastatic rhabdomyosarcoma, osteosarcoma and other metastatic sarcomas[67,68].

Although commercial cord banks promote cord banking to parents for the possible use for the treatment of childhood leukaemia, in 15 years of commercial cord blood banking only one case of autologous cord blood transplantation for acute lymphocytic leukaemia (ALL) has been reported in the medical literature, and that was in 2007 (REF. 52). This case was a 3-year-old girl with a central nervous system relapse. She was treated with systemic chemotherapy and myeloablative chemoradiotherapy and an autologous cord blood stem cell transplant. Correspondence following publication criticized the choice of treatment, as this patient might have been treated successfully without an autologous transplant[69]. It is possible that having a cord available in this case biased management decisions, and the correspondents also expressed concern regarding a potential conflict of interest, given that one author was an employee of the commercial cord bank[69]. This single case report, which is now widely quoted on commercial cord bank websites, also contains erroneous speculation on potential frequency of haematopoietic stem cell transplantation in childhood: it states a likelihood of 1:2,000, but, importantly, the authors do not distinguish between allogeneic and autologous transplantation (see below).

Autologous stem cell transplants also have no role in the management of ALL at initial diagnosis or at relapse, and have no proven benefit over intensified chemotherapy[46]. Autologous transplantation provides no GVL, and is inferior to allogeneic marrow and cord blood transplantation[46].

Preleukaemic cells in cord blood. Several recent reports of donor-derived leukaemia following allogeneic cord blood transplantation suggests a potential risk exists of disease 'recurrence' after transplantation with cord blood[70–74]. Ample evidence exists suggesting certain chromosomal translocations and fusion genes that characterize childhood leukaemia develop prenatally, are detectable in the cord blood at birth, and are probably initiating events in leukaemogenesis[75–77]. However, the presence of detectable preleukaemic translocations and fusion genes at birth are not on their own sufficient to cause leukaemia, and clearly other postnatal events are necessary to transform a preleukaemic stem cell into leukaemia[77].

The potential risk that these preleukaemia genetic events pose is the subject of debate, but this risk has been dismissed by several commercial cord banks because leukaemia-associated transcripts from fusion genes such as *BCR–ABL* are readily amplified from the peripheral blood of healthy adults[78–80]. However, the *BCR–ABL* transcript is detected at very low levels (fewer than 10 positive cells per 10^8), is not seen in cord blood, and most probably arises from illegitimate recombination within normal circulating white cells, and not from a population of preleukaemic stem cells. By contrast, the *TEL–AML* and *AML1–ETO* fusion genes of childhood lymphoblastic and myeloid leukaemia are detectable in cord blood and in some cases, but not all, this is associated with the development of leukaemia and production of in-frame transcripts in abundance, suggesting the presence of preleukaemic stem cell clones[73,76,77]. These recent findings indicate that we need to clearly understand the mechanisms of conversion of a preleukaemic cell into a leukaemic one, but the benefits of allogeneic cord blood transplantation clearly outweigh the risks of donor cell leukaemia[74].

A biological insurance

Biological insurance is a term used by many of the commercial cord banks and backed up by probabilities of use that range from a 1:400 lifetime chance of needing an autologous transplant[81] to 1:1,000–1:2,000 based on a previously published estimate of haematopoietic stem cell transplantation in childhood of 1:2,700 (REF. 82). Other previous estimates have suggested probabilities of use of between 1:20,000 to 1:200,000 depending on the age range, disease spectrum and type of transplant[83]. However, if autologous cord transplantation was as common as inferred, one would expect many more published clinical reports, so what is the best current estimate for probability of use of autologous banked umbilical cord blood in the first 20 years of life? As there are no current indications for autologous transplantation to treat genetic metabolic disorders, for gene therapy or for stem cell regenerative therapies, estimates are based on the likelihood of autologous cord blood transplantation for the treatment of cancer and acquired bone marrow failure syndromes.

Collaborative European cancer registry data recently reported the population-based frequency of cancer in children (1–14 years), and adolescents (15–20 years) diagnosed across Europe between 1978 and 1997. The total age-standardized incidence of cancer in children was 138 per million, and the total incidence in adolescents was 169 per million, giving pan-European population-based frequencies of 1:514 and 1:1,075, respectively[84,85]. Of the diagnoses most likely to require an allogeneic or autologous stem cell transplant, acute leukaemia accounts for 31% of childhood cancer diagnoses, 81% being ALL, whereas neuroblastoma occurs in 7% of cases and lymphoma in 9% (REF. 85).

When considering the probability of use it is necessary to consider that the overall cure rate for all cancers in this age group, including leukaemia, solid tumours, brain tumours and lymphomas, is approximately 75–80% using standard chemotherapy, radiotherapy and surgery alone. Just two cancer diagnoses, acute leukaemia and neuroblastoma, account for the majority of stem cell transplant procedures in childhood. For acute leukaemia, the population frequency in childhood is 1:1,650, with an 85% cure rate without stem cell transplantation[85]. Of the 15% who relapse, only half will need an allogeneic stem cell transplant, the rest being salvaged with chemoradiotherapy, giving a population frequency for stem cell transplantation in childhood leukaemia of 1:22,000. Moreover, as discussed above, autologous stem cell transplantation is not routinely indicated in relapsed leukaemia.

Neuroblastoma occurs in 1:7,300 children[86], 50% of whom have advanced-stage disease at diagnosis and require consolidation treatment with an autologous stem cell transplant[55], so the population-based frequency for autologous transplantation for neuroblastoma is approximately 1:15,000. Lymphomas (Hodgkin and non-Hodgkin), account for 9% of childhood cancer (1:5,700) and have a 90% cure rate with contemporary chemoradiotherapy[85]. Half of relapsed lymphoma is salvaged without

a stem cell transplant, and of the remainder both allogeneic and autologous transplants may be indicated with a population-based frequency of approximately 1:50,000. Of the remaining childhood cancers most are curable with standard therapy alone, but small numbers will benefit from autologous transplantation at relapse. However, autologous cord blood offers no additional clinical benefit over standard bone marrow harvests. Autologous stem cell transplantation has a limited role in the treatment of cancer in young adults, mostly for relapsed lymphoma or relapsed germ cell tumours.

Perhaps the only unequivocal benefit for an autologous cord blood transplant is the treatment of an acquired bone marrow failure syndrome such as acquired aplastic anaemia. With a frequency of 1:200,000, acquired aplastic anaemia is rare and in the absence of a sibling donor some 70% can be cured with immunotherapy alone and the remainder with unrelated cord or bone marrow transplants[87]. Only a single case report records autologous cord blood transplant for treatment of acquired aplastic anaemia[88].

At present the indications for autologous cord blood transplantation for childhood cancer are restricted to specific diagnoses, and the available epidemiological data suggests that the chance of using a cord blood sample for an autologous transplant is no better than 1:15,000 and, for the reasons discussed above, is almost certainly considerably less. Furthermore, in most cases in which an autologous stem cell transplant is indicated for cancer, stem cells can be harvested from bone marrow or peripheral blood before transplant and in this case autologous umbilical cord blood has no known clinical advantage over standard bone marrow-harvested stem cells.

This reanalysis supports several previously expressed opinions that autologous banking of cord blood as a biological insurance for the treatment of life-threatening diseases in children and young adults is not clinically justified because the chances of ever using it are remote. The absence of published peer-reviewed evidence raises the serious ethical concern of a failure to inform prospective parents about the lack of future benefit for autologous cord banking[7,10,22].

Marketing, ethics and public policy

Many would argue that commercial cord blood banking represents a considerable 'medical industry' that markets a service to parents and health-care providers as a leading-edge medical technology. Attempts to justify this are based on the success of unrelated public domain banking and allogeneic cord blood transplantation, and not on the use of autologous cord transplantation, the efficacy of which remains unproven.

Many have expressed the view that expectant parents are vulnerable to the marketing of commercial cord banks, which appears exploitative as it engenders as sense of guilt to do the best for their child, commonly using statements such as "a once in a lifetime opportunity", "storing your baby's umbilical cord blood could save their life", and "don't let a precious resource go to waste". Few parents or their health care providers will have access to the specialist information to understand the difference between private and public cord blood banking, which requires a greater degree of understanding and knowledge than can reasonably be expected from the lay public when confronted with information lacking independent authority. Even non-specialist medical and scientific professionals do not necessarily have sufficient information to provide parents with independent and accurate advice.

For many of the reasons discussed above, commercial cord blood banking has been criticized by many organizations, including the European Union Group on the Ethics of Science and New Technologies, the French National Consultative Ethics Committee for Health and Life Sciences, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynaecologists and the World Marrow Donor Association[9,10,22,89-91]. An absence of published data is not simply an academic criticism, because the information provided by commercial cord banks is used by parents to give informed consent for a procedure done at birth, on behalf of their child. Therefore, this information needs to be scientifically accurate, otherwise it is easy to suggest that parents are being misled or that the likely need for autologous cord blood transplants is being misrepresented.

Banking on stem cells

Public banking of umbilical cord blood for allogeneic stem cell transplantation is a proven and well-established therapy providing an immunologically naive source of haematopoietic stem cells for unrelated patients, especially where tissue matching is an issue. Public cord blood banks should be supported, especially in communities underrepresented on standard bone marrow donor registries, such as ethnic minorities.

When private banking began 15 years ago, public cord and bone marrow donor panels were limited in number and autologous transplants were being used at the time for treatment of acute leukaemia as well as solid tumours. However, the results of contemporary chemotherapy and the proven benefit of GVL from allogeneic stem cell transplants restricts the role of autologous stem cell transplantation to a limited number of clinical indications. With this in mind, commercial cord banks currently offer a service for the treatment of diseases for which proven alternatives are now available. Moreover, speculative banking for future stem cell therapies might well be made obsolete by the rapid advances in stem cell technology, such as the development of induced pluripotent stem cells (BOX 4).

Despite all past and current scientific and ethical criticism, there seems to be a somewhat passive acceptance of commercial cord banking by regulatory authorities while public banking struggles for support. Clearly, umbilical cord blood banking is viewed as both for the public good and for private profit.

Michael J. Sullivan is at the Children's Cancer Research Group, and Children's Haematology Oncology Centre, Department of Paediatrics, Christchurch School of Medicine, University of Otago, 2 Riccarton Ave, Christchurch, 8005, New Zealand.
e-mail: michael.sullivan@otago.ac.nz

doi:10.1038/nrc2418
Published online 12 June 2008

1. Barker, J. N. & Wagner, J. E. Umbilical-cord blood transplantation for the treatment of cancer. *Nature Rev. Cancer* **3**, 526–532 (2003).
2. Gluckman, E. & Rocha, V. History of the clinical use of umbilical cord blood hematopoietic cells. *Cytotherapy* **7**, 219–227 (2005).
3. Rubinstein, P. Why cord blood? *Human Immunol.* **67**, 398–404 (2006).
4. Cord Blood Registry [online] http://www.cordblood.com/ (2007).
5. Annas, G. J. Waste and longing — The legal status of placental-blood banking. *N. Engl. J. Med.* **340**, 1521–1524 (1999).
6. Burgio, G. R. & Locatelli, F. Transplant of bone marrow and cord blood hematopoietic stem cells in pediatric practice, revisited according to the fundamental principles of bioethics. *Bone Marrow Transplant.* **19**, 1163–1168 (1997).
7. Fisk, N. M., Roberts, I. A., Markwald, R. & Mironov, V. Can routine commercial cord blood banking be scientifically and ethically justified? *PLoS Med.* **2**, e44 (2005).
8. Sugarman, J. *et al.* Ethical issues in umbilical cord blood banking. Working Group on Ethical Issues in Umbilical Cord Blood Banking. *JAMA* **278**, 938–943 (1997).
9. American Academy of Pediatrics WGOCBB. Cord blood banking for potential future transplantation: subject review. American Academy of Pediatrics. Work Group on Cord Blood Banking. *Pediatrics* **104**, 116–118 (1999).
10. Puigdomench-Rosell, P., Virt, G., for the European Group on Ethics in Science and New Technologies. Ethical aspects of umbilical cord blood banking.

European Group on Ethics in Science and New Technologies, European Commission [online] http://ec.europa.eu/european_group_ethics/publications/docs/publop19_en.pdf (2004).
11. Barker, J. N. & Wagner, J. E. Umbilical cord blood transplantation: current practice and future innovations. *Crit. Rev. Oncol. Hematol.* **48**, 35–43 (2003).
12. Benito, A. I., Diaz, M. A., Gonzalez-Vicent, M., Sevilla, J. & Madero, L. Hematopoietic stem cell transplantation using umbilical cord blood progenitors: review of current clinical results. *Bone Marrow Transplant.* **33**, 675–690 (2004).
13. Eapen, M. *et al.* Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. [see comment] *Lancet* **369**, 1947–1954 (2007).
14. Hwang, W. Y. *et al.* A meta-analysis of unrelated donor umbilical cord blood transplantation versus unrelated donor bone marrow transplantation in adult and pediatric patients. *Biol. Blood Marrow Transplant.* **13**, 444–453 (2007).
15. Laughlin, M. J. *et al.* Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. *N. Engl. J. Med.* **351**, 2265–2275 (2004).
16. Mao, P. *et al.* Umbilical cord blood transplant for adult patients with severe aplastic anemia using anti-lymphocyte globulin and cyclophosphamide as conditioning therapy. *Bone Marrow Transplant.* **33**, 33–38 (2004).
17. Ooi, J. *et al.* Unrelated cord blood transplantation for adult patients with *de novo* acute myeloid leukemia. *Blood* **103**, 489–491 (2004).
18. Ooi, J. *et al.* Unrelated cord blood transplantation for adult patients with acute lymphoblastic leukemia. *Leukemia* **18**, 1905–1907 (2004).
19. Rocha, V. *et al.* Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. *Blood* **97**, 2962–2971 (2001).
20. Rubinstein, P. & Stevens, C. E. Placental blood for bone marrow replacement: the New York Blood Center's program and clinical results. *Bailliere's Best Pract. Clin. Haematol.* **13**, 565–584 (2000).
21. Rubinstein, P. *et al.* Outcomes among 562 recipients of placental-blood transplants from unrelated donors. *N. Engl. J. Med.* **339**, 1565–1577 (1998).
22. American Academy of Pediatrics Section on Hematology Oncology, American Academy of Pediatrics Section on allergy Immunology, Lubin, B. H. & Shearer, W. T. Cord blood banking for potential future transplantation. *Pediatrics* **119**, 165–170 (2007).
23. Armson, B. A. & Maternal/Fetal Medicine Committee SOOAGOC. Umbilical cord blood banking: implications for perinatal care providers. *J. Obstet. Gynaecol. Can.* **27**, 263–290 (2005) [erratum appears in *J. Obstet. Gynaecol. Can.* **27**, 673].
24. Eaton, L. Many cord blood banks' claims are unfounded, says Royal College. *BMJ* **332**, 1411 (2006).
25. Edozien, L. C. NHS maternity units should not encourage commercial banking of umbilical cord blood. *BMJ* **333**, 801–804 (2006) [see comment].
26. Kurtzberg, J., Lyerly, A. D. & Sugarman, J. Untying the Gordian knot: policies, practices, and ethical issues related to banking of umbilical cord blood. *J. Clin. Invest.* **115**, 2592–2597 (2005).
27. Steinbrook, R. The cord-blood-bank controversies. *N. Engl. J. Med.* **351**, 2255–2257 (2004).
28. Sullivan, M., Browett, P. & Patton, N. Private umbilical cord blood banking: a biological insurance of dubious future benefit! *N. Z. Med. J.* **118**, U1260 (2005) [see comment].
29. van Rood, J. J. & Oudshoorn, M. Eleven million donors in Bone Marrow Donors Worldwide! Time for reassessment? *Bone Marrow Transplant.* **41**, 1–9 (2008).
30. Rocha, V. & Locatelli, F. Searching for alternative hematopoietic stem cell donors for pediatric patients. *Bone Marrow Transplant.* **41**, 207–214 (2008).
31. Gluckman, E. *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.* **321**, 1174–1178 (1989).
32. Wall, D. A. Issues in the quality of umbilical cord blood stem cells for transplantation: challenges in cord blood banking quality management. *Transfusion* **45**, 826–828 (2005).
33. Anonymous. Umbilical cord blood banking Richard Branson's way. *Lancet* **369**, 437 (2007).
34. Garderet, L. *et al.* The umbilical cord blood αβ T-cell repertoire: characteristics of a polyclonal and naive but completely formed repertoire. *Blood* **91**, 340–346 (1998).
35. Rocha, V. *et al.* Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. Eurocord and International Bone Marrow Transplant Registry Working Committee on Alternative Donor and Stem Cell Sources. *N. Engl. J. Med.* **342**, 1846–1854 (2000).
36. Rocha, V., Gluckman, E. & Eurocord and European Blood and Marrow Transplant Group. Clinical use of umbilical cord blood hematopoietic stem cells. *Biol. Blood Marrow Transplant.* **12**, 34–41 (2006).
37. Schoemans, H. *et al.* Adult umbilical cord blood transplantation: a comprehensive review. *Bone Marrow Transplant.* **38**, 83–93 (2006).
38. Broxmeyer, H. E. Biology of cord blood cells and future prospects for enhanced clinical benefit. *Cytotherapy* **7**, 209–218 (2005).
39. Wexler, S. A. *et al.* Adult bone marrow is a rich source of human mesenchymal 'stem' cells but umbilical cord and mobilized adult blood are not. *Br. J. Haematol.* **121**, 368–374 (2003).
40. He, Q., Wan, C. & Li, G. Concise review: multipotent mesenchymal stromal cells in blood. *Stem Cells* **25**, 69–77 (2007).
41. Lennard, A. L. & Jackson, G. H. Stem cell transplantation. *BMJ* **321**, 433–437 (2000). [erratum appears in *BMJ* **321**,1331]
42. Prasad, V. K. & Kurtzberg, J. Emerging trends in transplantation of inherited metabolic diseases. *Bone Marrow Transplant.* **41**, 99–108 (2008).
43. Gluckman, E. & Wagner, J. E. Hematopoietic stem cell transplantation in childhood inherited bone marrow failure syndrome. *Bone Marrow Transplant.* **41**, 127–132 (2008).
44. Bhatia, M. & Walters, M. C. Hematopoietic cell transplantation for thalassemia and sickle cell disease: past, present and future. *Bone Marrow Transplant.* **41**, 109–117 (2008).
45. Dvorak, C. C. & Cowan, M. J. Hematopoietic stem cell transplantation for primary immunodeficiency disease. *Bone Marrow Transplant.* **41**, 119–126 (2008).
46. Hahn, T. *et al.* The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in children: an evidence-based review. *Biol. Blood Marrow Transplant.* **11**, 823–861 (2005).
47. Copelan, E. A. Hematopoietic stem-cell transplantation. *N. Engl. J. Med.* **354**, 1813–1826 (2006) [see comment].
48. Carella, A. M. & Bregni, M. Current role of allogeneic stem cell transplantation in breast cancer. *Ann. Oncol.* **18**, 1591–1593 (2007).
49. Rocha, V. *et al.* Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N. Engl. J. Med.* **351**, 2276–2285 (2004).
50. Ferreira, E., Pasternak, J., Bacal, N., de Campos Guerra, J. C. & Mitie Watanabe, F. Autologous cord blood transplantation. *Bone Marrow Transplant* **24**, 1041 (1999).
51. Friedrich, M. J. Growing role for umbilical cord blood. *JAMA* **292**, 2453–2454 (2004).
52. Hayani, A., Lampeter, E., Viswanatha, D., Morgan, D. & Salvi, S. N. First report of autologous cord blood transplantation in the treatment of a child with leukemia. *Pediatrics* **119**, e296–300 (2007).
53. Fish., J. D. & Grupp, S. A. Stem cell transplantation for neuroblastoma. *Bone Marrow Transplant.* **41**, 159–165 (2008).
54. Philip, T. *et al.* 1070 myeloablative megatherapy procedures followed by stem cell rescue for neuroblastoma: 17 years of European experience and conclusions. European Group for Blood and Marrow Transplant Registry Solid Tumour Working Party. *Eur. J. Cancer* **33**, 2130–2135 (1997).
55. Hartmann, O. *et al.* Prognostic factors in metastatic neuroblastoma in patients over 1 year of age treated with high-dose chemotherapy and stem cell transplantation: A multivariate analysis in 218 patients treated in a single institution. *Bone Marrow Transplant.* **23**, 789–795 (1999).
56. George, R. E. *et al.* High-risk neuroblastoma treated with tandem autologous peripheral-blood stem cell-supported transplantation: long-term survival update. *J. Clin. Oncol.* **24**, 2891–2896 (2006).
57. Burdach, S. *et al.* Allogeneic and autologous stem-cell transplantation in advanced Ewing tumors. An update after long-term follow-up from two centers of the European Intergroup study EICESS. Stem-Cell Transplant Programs at Dusseldorf University Medical Center, Germany and St. Anna Kinderspital, Vienna, Austria. *Ann. Oncol.* **11**, 1451–1462 (2000).
58. Burke, M. J., Walterhouse, D. O., Jacobsohn, D. A., Duerst, R. E. & Kletzel, M. Tandem high-dose chemotherapy with autologous peripheral hematopoietic progenitor cell rescue as consolidation therapy for patients with high-risk Ewing family tumors. *Pediatric Blood Cancer* **49**, 196–198 (2007) [see comment].
59. Dunkel, I. J. & Finlay, J. L. High-dose chemotherapy with autologous stem cell rescue for brain tumors. *Critical Rev. Oncol. Hematol.* **41**, 197–204 (2002).
60. Fagioli, F. *et al.* High-dose thiotepa and etoposide in children with poor-prognosis brain tumors. *Cancer* **100**, 2215–2221 (2004).
61. Lin, T. S. & Copelan, E. A. Autologous stem cell transplantation for non-Hodgkin's lymphoma. *Curr. Hematol. Rep.* **2**, 310–315 (2003).
62. Meyers, P. A. *et al.* High-dose melphalan, etoposide, total-body irradiation, and autologous stem-cell reconstitution as consolidation therapy for high-risk Ewing's sarcoma does not improve prognosis. *J. Clin. Oncol.* **19**, 2812–2820 (2001).
63. Thorarinsdottir, H. K. *et al.* Outcome for children < 4 years of age with malignant central nervous system tumors treated with high-dose chemotherapy and autologous stem cell rescue. *Pediatric Blood Cancer* **48**, 278–284 (2007).
64. Bradley, M. B. & Cairo, M. S. Stem cell transplantation for pediatric lymphoma: past, present and future. *Bone Marrow Transplant.* **41**, 149–158 (2008).
65. Marachelian, A., Butturini, A. & Finlay, J. Myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for childhood central nervous system tumors. *Bone Marrow Transplant.* **41**, 167–172 (2008).
66. Kremens, B. *et al.* High-dose chemotherapy with autologous stem cell rescue in children with nephroblastoma. *Bone Marrow Transplant.* **30**, 893–898 (2002).
67. Fagioli, F. *et al.* High-dose chemotherapy in the treatment of relapsed osteosarcoma: an Italian sarcoma group study. *J. Clin. Oncol.* **20**, 2150–2156 (2002).
68. Koscielniak, E. *et al.* Do patients with metastatic and recurrent rhabdomyosarcoma benefit from high-dose therapy with hematopoietic rescue? Report of the German/Austrian Pediatric Bone Marrow Transplantation Group. *Bone Marrow Transplant.* **19**, 227–231 (1997).
69. Urban, C. *et al.* Autologous cord blood transplantation in a child with acute lymphoblastic leukemia and central nervous system relapse [comment]. *Pediatrics* **119**, 1042–1043; author reply 1043 (2007).
70. Zipursky, A. Fetal origin of leukemia and autologous cord blood transfusions. *Pediatric Res.* **47**, 574 (2000).
71. Ando, T. *et al.* Donor cell-derived acute myeloid leukemia after unrelated umbilical cord blood transplantation. *Leukemia* **20**, 744–745 (2006) [see comment].
72. Fraser, C. J. *et al.* First report of donor cell-derived acute leukemia as a complication of umbilical cord blood transplantation. *Blood* **106**, 4377–4380 (2005).
73. Greaves, M. Cord blood donor leukaemia in recipients. *Leukemia* **20**, 1633–1664 (2006).
74. Matsunaga, T., *et al.* Donor cell derived acute myeloid leukemia after allogeneic cord blood transplantation in a patient with adult T-cell lymphoma. *Am. J. Hematol.* **79**, 294–298 (2005).
75. Greaves, M. Pre-natal origins of childhood leukemia. *Rev. Clin. Exp. Hematol.* **7**, 233–245 (2003).
76. Greaves, M. F. & Wiemels, J. Origins of chromosome translocations in childhood leukaemia. *Nature Rev. Cancer* **3**, 1–11 (2003).
77. Mori, H. *et al.* Chromosome translocations and covert leukemic clones are generated during normal fetal development. *Proc. Natl Acad. Sci. USA* **99**, 8242–8247 (2002).
78. Biernaux, C., Loos, M., Sels, A., Huez, G. & Stryckmans, P. Detection of major bcr-abl gene expression at a very low level in blood cells of some healthy individuals. *Blood* **86**, 3118–3122 (1995).
79. Biernaux, C., Sels, A., Huez, G. & Stryckmans, P. Very low level of major BCR–ABL expression in blood of some healthy individuals. *Bone Marrow Transplant.* **17** (Suppl. 3), S45–47 (1996).

80. Bose, S., Deininger, M., Gora-Tybor, J., Goldman, J. M. & Melo, J. V. The presence of typical and atypical BCR–ABL fusion genes in leukocytes of normal individuals: biologic significance and implications for the assessment of minimal residual disease. *Blood* **92**, 3362–3367 (1998).
81. Pasquini, M. C., Logan, B. R., Verter, F., Horowitz, M. M. & Nietfeld, J. J. The likelihood of hematopoietic stem cell transplantation (HCT) in the United States: implications for umbilical cord blood storage. *ASH Ann. Meeting Abstracts* **106**, 1330 (2005).
82. Johnson, F. L. Placental blood transplantation and autologous banking — caveat emptor. *J. Pediatric Hematol. Oncol.* **19**, 183–186 (1997).
83. Kline, R. D. Whose blood is it, anyway. *Sci. Am.* **4**, 30–37 (2001).
84. Stiller, C. A. *et al.* Cancer incidence and survival in European adolescents (1978–1997). Report from the Automated Childhood Cancer Information System project. *Eur. J. Cancer* **42**, 2006–2018 (2006).
85. Stiller, C. A. *et al.* Geographical patterns of childhood cancer incidence in Europe, 1988–1997 Report from the Automated Childhood Cancer Information System project. *Eur. J. Cancer* **42**, 1952–1960 (2006).
86. Spix, C., Pastore, G., Sankila, R., Stiller, C. A. & Steliarova-Foucher, E. Neuroblastoma incidence and survival in European children (1978–1997): report from the Automated Childhood Cancer Information System project. *Eur. J. Cancer* **42**, 2081–2091 (2006).
87. Armand, P. & Antin, J. H. Allogeneic stem cell transplantation for aplastic anemia. *Biol. Blood Marrow Transplant.* **13**, 505–516 (2007).
88. Fruchtman, S. M. *et al.* The successful treatment of severe aplastic anemia with autologous cord blood transplantation. *Biol. Blood Marrow Transplant.* **10**, 741–742 (2004).
89. American College of Obstetricians and Gynecologists. Routine storage of umbilical cord blood for potential future transplantation. *Int. J. Gynaecol. Obstet.* **58**, 257–259 (1997).
90. French National Consultative Ethics Committee for Health and Life Sciences. Umbilical cord blood banks for autologous use or for research. Opinion number 74 [online] http://www.ccne-ethique.fr/docs/fr/avis074.pdf (2002).
91. Royal College of Obstetricians and Gynaecologists Scientific Advisory Committee. Umbilical cord blood banking. Opinion paper 2 revised [online] http://www.rcog.org.uk/index.asp?PageID=545 (2006).
92. Grewal, S. S., Kahn, J. P., MacMillan, M. L., Ramsay, N. K. & Wagner, J. E. Successful hematopoietic stem cell transplantation for Fanconi anemia from an unaffected HLA-genotype-identical sibling selected using preimplantation genetic diagnosis. *Blood* **103**, 1147–1151 (2004).
93. Mazur, M., Kurtzberg, J., Halperin, E., Ciocci, G. & Szabolcs, P. Transplantation of a child with sickle cell anemia with an unrelated cord blood unit after reduced intensity conditioning. *J. Pediatric Hematol. Oncol.* **28**, 840–844 (2006).
94. Picardi, A. *et al.* Unrelated cord blood transplantation for children with high risk myelodysplastic syndromes. *Haematologica* **89**, ELT08 (2004).
95. Yesilipek, M. A. Stem cell transplantation in hemoglobinopathies. *Hemoglobin* **31**, 251–256 (2007).
96. Cibelli, J. Development: Is therapeutic cloning dead? *Science* **318**, 1879–1880 (2007).
97. Yamanaka, S. Strategies and new developments in the generation of patient-specific pluripotent stem cells. *Cell Stem Cell* **1**, 39–49 (2007).
98. Maherali, N., *et al.* Directly reprogrammed fibroblasts show global epigenetic remodeling and widespread tissue contribution. *Cell Stem Cell* **1**, 55–70 (2007).
99. Park, I. H. *et al.* Reprogramming of human somatic cells to pluripotency with defined factors. *Nature* **451**, 141–146 (2008).
100. Wernig, M. *et al. In vitro* reprogramming of fibroblasts into a pluripotent ES-cell-like state. *Nature* **448**, 318–324 (2007) [see comment].
101. Yu, J. *et al.* Induced pluripotent stem cell lines derived from human somatic cells. *Science* **318**, 1917–1920 (2007).

Acknowledgements
The author thanks R. Corbett, A. Turnbull and S. Beasley for their support and advice.

FURTHER INFORMATION

M. J. Sullivan's homepage: http://www.chmeds.ac.nz/research/ccrg/
American Society for Blood and Marrow Transplantation (ASBMT): http://www.asbmt.org/
Bone Marrow Donors Worldwide (BMDW): http://www.bmdw.org/
Caitlin Raymond International Registry: http://www.crir.org/
Center for International Blood and Marrow Transplant research (CIRBMT): http://www.cibmtr.org/
Cord Blood Forum: http://www.cordbloodforum.org/
Eurocord: http://www.eurocord.org/
European Group for blood and marrow transplantation (EBMT): http://www.ebmt.org/
Foundation for Accreditation of Cellular Therapies (FACT): http://www.factwebsite.org/
Joint Accreditation Committee: http://www.jacie.org/
National Marrow Donor Program (NMDP): http://www.marrow.org/
NetCord: https://www.netcord.org/status.html
Parent's Guide to Cord Blood: http://parentsguidecordblood.org/
World Marrow Donor Association: http://www.worldmarrow.org/

DATABASES

National Cancer Institute: http://www.cancer.gov/
acute lymphocytic leukaemia | graft-versus-host disease | leukaemia | lymphoma | multiple myeloma | neuroblastoma | non-Hodgkin lymphoma | osteosarcoma | rhabdomyosarcoma | Wilms tumour
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Fanconi anaemia

ALL LINKS ARE ACTIVE IN THE ONLINE PDF