Umbilical Cord Blood and Cancer Biology Research Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

The following introduces recent reports as references in the related studies.

Barker, J. N. and J. E. Wagner (2003). "Umbilical-cord blood transplantation for the treatment of cancer." Nat Rev Cancer **3**(7): 526-532.

Haematopoietic stem-cell transplantation is used to treat many haematological cancers, but is limited by the lack of suitable bone-marrow donors, the risk of graft-versus-host disease (GVHD) and slow immune reconstitution. Umbilical-cord blood is an alternative source of haematopoietic stem cells that has recently been tested in both child and adult cancer patients. These studies have identified several advantages to umbilical-cord cell transplantation, including a lower incidence of GVHD. Umbilical-cord blood is therefore a promising alternative to bone-marrow-derived stem cells.

Bhattacharya, N. (2006). "A study of placental umbilical cord whole blood transfusion in 72 patients with anemia and emaciation in the background of cancer." Eur J Gynaecol Oncol **27**(2): 155-161.

In the under-resourced world, transfusion to advanced oncological patients involves two major problems, i.e., (a) transfusion transmitted disease, and (b) infrastructural deficiency. Many hospitals cannot cope with the specialized requirements of immunocompromised cancer victims, for instance, leucoreduction, selective apheresis, irradiation of the blood, viral inactivation of the blood by solvent and/or detergent treatment or photochemical inactivation using psoralen or long wavelength ultraviolet light and cytomegalovirus safe blood. The exorbitant cost of red blood cell (RBC) substitutes like hemoglobin-based oxygen carriers or perflurocarbon emulsions, liposome encapsulated hemoglobin, is simply unacceptable for an average oncological patient in the developing world. Moreover, it should be underscored that none of the total blood functions are replaced by any available so-called blood substitute, the primary function of which is oxygen delivery and volume expansion only. A more accurate term should be red cell substitute. Cord blood, because of its rich mix of fetal and adult hemoglobin, platelet and white blood cell (WBC) count, and plasma filled with cytokine and growth factors--as well as its hypoantigenic nature and altered metabolic profile--has all the potential of a real and safe alternative to adult blood during emergencies or any etiology of blood loss. In the present series, the collection of cord blood varied from 54 ml-128 ml, mean 82 ml +/- 7.6 ml SD; mean packed cell volume 48 +/- 4.1% SD; mean percent hemoglobin concentration 16.4 g/dl +/- 1.6 g/dl SD. Not a single case of immunological or non immunological reaction has been encountered so far after transfusion of cord blood to cancer patients with percent of hemoglobin 8 g/dl or less. It appears that the medical fraternity can safely use this precious gift of nature-- which is free from infection, hypoantigenic with altered metabolic profile, filled with growth

factors and cytokine-filled plasma, and has the potential of a higher oxygen carrying capacity than adult blood--as an emergency source of blood for the management of advanced cancer cases with anemia.

Cany, J., et al. (2015). "Umbilical cord blood-derived cellular products for cancer immunotherapy." Cytotherapy **17**(6): 739-748.

Although the vast majority of experience with umbilical cord blood (CB) centers on hematopoietic reconstitution, a recent surge in the knowledge of CB cell subpopulations as well as advances in ex vivo culture technology have expanded the potential of this rich resource. Because CB has the capacity to generate the entire hematopoietic system, we now have a new source for natural killer, dendritic and T cells for therapeutic use against malignancies. This Review will focus on cellular immunotherapies derived from CB. Expansion techniques, ongoing clinical trials and future directions for this new dimension of CB application are also discussed.

Ende, N., et al. (2006). "Administration of human umbilical cord blood cells delays the onset of prostate cancer and increases the lifespan of the TRAMP mouse." Cancer Lett **231**(1): 123-128.

Stem cell transplantation to improve the onset and survival of animals or humans with prostate cancer has not been studied adequately. In this study, we examined whether intravenous administration of human umbilical cord blood (HUCB) mononuclear cells into TRAMP (transgenic adenocarcinoma of the mouse prostate) mice can delay the onset of prostate cancer and improve survival of these mice before and after the development of cancer. Twenty TRAMP mice were randomly divided into 2 groups. One group of 10 mice received 200 x10(6) HUCB mononuclear cells retro-orbitally into the venous plexus at the age of 6 weeks. Another group of 10 mice did not receive HUCB cells and served as control mice. The presence of tumor was detected by abdominal palpation, which was confirmed by biopsy. When 4 of the 10 control mice developed the tumor, they were treated with the same dose of HUCB cells. Either at the time of death or sacrifice, various tissues were examined for the presence of HUCB cell total RNA by reverse transcriptase PCR. Also, the tissues were examined histologically for the presence of metastasis and carcinoma. Kaplan-Meier survival plots were used to assess the lifespan of the mice. The data show that the control mice developed the tumor much earlier than the treated mice (control vs treated: 238+/-38 vs 311+/-40 days; $P<0.001$). Also, transplantation of HUCB cells either before or after the development of tumor significantly increased the life span compared to that of control mice. Persistence of human RNA either in blood or spleen was associated with prolonged survival. No graft vs host disease was observed in any of the mice. In conclusion, transplantation of HUCB mononuclear cells via intravenous administration into TRAMP mice retards not only the development of prostate cancer but also increases the lifespan of these mice.

Hoogstad-van Evert, J. S., et al. (2017). "Umbilical cord blood CD34(+) progenitor-derived NK cells efficiently kill ovarian cancer spheroids and intraperitoneal tumors in NOD/SCID/IL2Rg (null) mice." Oncoimmunology **6**(8): e1320630.

Adoptive transfer of allogeneic natural killer (NK) cells is an attractive therapy approach against ovarian carcinoma. Here, we evaluated the potency of highly active NK cells derived from human CD34+ haematopoietic stem and progenitor cells (HSPC) to infiltrate and mediate killing of human ovarian cancer spheroids using an in vivo-like model system and mouse xenograft model. These CD56+Perforin+ HSPC-NK cells were generated under stroma-free conditions in the presence of StemRegenin-1, IL-15, and IL-12, and exerted efficient cytolytic activity and IFNgamma production toward ovarian cancer monolayer cultures. Live-imaging confocal microscopy demonstrated that these HSPC-NK cells actively migrate, infiltrate, and mediate tumor cell killing in a three-dimensional multicellular ovarian cancer spheroid. Infiltration of up to 30% of total HSPC-NK cells within 8 h resulted in robust tumor spheroid destruction. Furthermore, intraperitoneal HSPC-NK cell infusions in NOD/SCID-IL2Rgamma (null) (NSG) mice bearing ovarian carcinoma significantly reduced tumor progression. These findings demonstrate that highly functional HSPC-NK cells efficiently destruct ovarian carcinoma spheroids in vitro and kill intraperitoneal ovarian tumors in vivo, providing great promise for effective immunotherapy through intraperitoneal HSPC-NK cell adoptive transfer in ovarian carcinoma patients.

Hu, W., et al. (2011). "Augmenting therapy of ovarian cancer efficacy by secreting IL-21 human umbilical cord blood stem cells in nude mice." Cell Transplant **20**(5): 669-680.

In the present study, CD34(+) human umbilical cord blood stem cells (UCBSCs) were engineered to express interleukin-21 (IL-21) and then were transplanted into A2780 ovarian cancer xenograft-bearing Balb/c nude mice. The therapeutic efficacy of this procedure on ovarian cancer was evaluated. The findings from the study indicated that UCBSCs did not form gross or histological teratomas until up to 70 days postinjection. The CD34(+) UCBSC-IL-21 therapy showed a consistent effect in the ovarian cancer of the

treated mice, delaying the tumor appearance, reducing the tumor sizes, and extending life expectancy. The efficacy was attributable to keeping CD34(+) UCBSC-IL-21 in the neoplastic tissues for more than 21 days. The secreted IL-21 not only increased the quantity of CD11a (+) and CD56(+) NK cells but also increased NK cell cytotoxicities to YAC-1 cells and A2780 cells, respectively. The efficacy was also associated with enhancing the levels of IFN-gamma, IL-4, and TNF-alpha in the mice as well as the high expressions of the NKG2D and MIC A/B molecules in the tumor tissues. This study suggested that transferring CD34(+) UCBSC-IL-21 into the nude mice was safe and feasible in ovarian cancer therapy, and that the method would be a promising new strategy for clinical treatment of ovarian cancer.

Jiang, Z., et al. (2008). "Local effects of retrovirally transduced endostatin-expressing human umbilical cord blood CD34+ cells on transplanted malignancy in a mouse model of hepatic cancer." Cell Transplant **17**(8): 969-975.

Antiangiogenesis has been exploited as an effective approach to inhibit the growth of solid tumors. This technique has been evaluated using various vectors in several xenograft animal models to demonstrate the efficacy of endostatin gene therapy against cancer growth. However, previous studies have not examined the use of cord blood CD34+ cells as endostatin-producing cells for gene therapy against hepatoma. This exploratory study was done to investigate the local effects of CD34+ cells transduced with the endostatin gene on a mouse xenograft tumor model. The human endostatin gene was transferred into CD34+ cells using the recombinant retrovirus plasmid, pLncx/endo. Expression was verified by RT-PCR and Western blot analyses, confirming the stable expression and secretion of endostatin from the transferred CD34+ cells. The proliferation of vascular endothelial cells was evaluated by MTT assay and found to decrease by about 59.9% when treated with the supernatant of cultured transfected CD34+ cells in vitro. These genetically modified cord blood CD34+ cells were implanted intratumorally and tumor regression was evaluated after 2 weeks. The average size of a xenograft tumor in the CD34+/endo group was reduced 31.39% compared to that in the untreated mice or those transplanted with CD34+ cells transduced with a control vector. The microvascular density of the tumor decreased 62.45% in the treated group. The expression of proliferation cell nuclear antigen (PCNA) also decreased significantly in the treated group. Moreover, the apoptotic index (AI) of tumors, as evaluated by TUNEL staining, was significantly enhanced in the treatment group. Our findings indicate that angiogenesis of the xenograft tumor in mice may be inhibited by local administration of genetically modified CD34+ cells expressing the endostatin gene. This novel approach may lead to a new direction of cell-based gene therapy for malignancy.

Joshi, S. S., et al. (2000). "Antitumor therapeutic potential of activated human umbilical cord blood cells against leukemia and breast cancer." Clin Cancer Res **6**(11): 4351-4358.

In this study, in vitro and in vivo antitumor effects of mononuclear cells from human umbilical cord blood cells (UCBCs) and peripheral blood stem cells (PBCs) harvest obtained by leukapheresis were compared. Interleukin 2 (IL-2)-activated mononuclear cells from UCBCs showed increased cytotoxicity against K562 and Raji hematopoietic malignant cells compared with PBCs ($P < 0.05$). After IL-2 activation, both UCBCs and PBCs showed significant cytotoxicity against MDA-231 human breast cancer cells. The UCBC population involved in this antitumor activity appeared to be CD56+ natural killer precursors. The cytotoxicity of UCBCs was inhibited in the absence of Ca2+ ($P < 0.05$), supporting a perforin/granzyme-mediated target of cell lysis. In addition, antibodies to Fas ligand blocked cytotoxic activity, suggesting that some of the antitumor cytotoxicity was Fas ligand mediated. In vivo antitumor effects of UCBCs and PBCs were studied using a human leukemic cell-bearing severe combined immunodeficient mouse model. There was a significant increase in the survival of K562 leukemia-bearing mice that also received 5 million in vitro IL-2-activated UCBCs or PBCs i.v. on days 3 and day 5 after tumor transplantation compared with untreated mice ($P < 0.01$). Similar antitumor cytotoxicity of UCBCs and PBCs was also observed against MDA-231 human breast cancer grown in severe combined immunodeficient mice ($P < 0.01$). These studies suggest that IL-2-activated UCBCs may be a useful source of cellular therapy for patients with hematological malignancies and breast cancer.

Kumar, J., et al. (2015). "Umbilical cord blood-derived CD11c (+) dendritic cells could serve as an alternative allogeneic source of dendritic cells for cancer immunotherapy." Stem Cell Res Ther **6**: 184.

INTRODUCTION: Allogenic dendritic cells (DCs) generated from healthy donors, who are complete or partially HLA-matched, have been used for clinical trials. One of the sources for allogenic DCs is umbilical cord blood (UCB) cells. However, as far as cord blood cells are concerned, looking at their naive nature, there is a concern as to whether the DCs generated from them will have enough potential to elicit a proper T cell response. For this, we compared CD11c (+) UCB-DCs/ Cytotoxic T lymphocytes (CTLs) with the conventional source, i.e. peripheral

blood (PBL) monocyte DCs/CTLs, using various parameters. METHODS: CD11c (+) DCs generated from the two sources were compared morphologically, phenotypically and functionally. Functional assays included antigen uptake, chemotactic migration and MLR (mixed lymphocyte reaction). The CTLs generated were examined for the activation markers, granzyme A & granzyme B, and IFN-gamma secretion. MUC1 (STAPPVHNV) peptide-specific CTLs were quantified by Streptamer staining. In vitro CTL activity was assessed by their efficiency in killing MCF-7 cells. For in vivo CTL assay, a xenograft of MCF-7-luc-F5 cells in female NOD/SCID mice was employed. Regression of tumors in mice was monitored using an in vivo imaging system before and after ten days of CTL infusion. Statistical analysis of all the experiments between the two groups was evaluated by one-way ANOVA. RESULTS: The CD11c (+) DCs from the two sources were morphologically and phenotypically similar. Their capacity to uptake antigen, migration towards CCL-19 and MLR activity were equivalent. UCB-CTLs had significantly higher levels of activation markers, number of MUC1 specific CTLs, IFN-gamma secretion and IL-12p70/IL-10 ratio than that of PBL-CTLs. Hematoxylin and Eosin-stained tumor sections showed T cell infiltration, which was further confirmed by immunofluorescence staining. In vivo CTL activity was found to be similar with the two sources. CONCLUSIONS: Our data demonstrate that CD11c (+) UCB-DCs/CTLs are as potent as standard CD11c (+) PBL-DC/CTLs and could therefore be used as an allogenic source for therapeutic purposes. The findings of this study could help in taking us one step closer towards the personalized therapy using DC based cancer vaccines.

Li, Q. L., et al. (2008). "Exvivo experiments of human ovarian cancer ascites-derived exosomes presented by dendritic cells derived from umbilical cord blood for immunotherapy treatment." Clin Med Oncol **2**: 461-467.

OBJECTIVES: Exosomes, a type of membrane vesicles, released from tumor cells have been shown to be capable of transferring tumor antigens to dendritic cells and activating specific cytotoxic T-lymphocytes. Recent work has demonstrated the presence of high numbers of exosomes in malignant effusions. Umbilical cord blood (UCB) is a rich source of hematopoietic stem cells and from which a significant number of dendritic cells can be produced. We hypothesized that the exosomes released from metastatic ovarian carcinoma were able to present tumor specific antigen to dendritic cells derived from unrelated umbilical cord blood, then could stimulate resting T cells to differentiate and induce effective cytotoxicity. STUDY DESIGN: Exosomes were isolated by ultracentrifugation of malignant ascites from ovarian cancer patients (n = 10). Purified exosomes were further characterized by Western blot analyses and immunoelectronic microscopy. Dendritic cells were collected from unrelated umbilical cord blood and cultured in the presence of GM-CSF, IL-4 and TNF-alpha. Resting T cells were mixed with dentritic cells previously primed with exosomes and the cytotoxicity were measured by MTT method. T cells were activated by DCs presented with exosomes. RESULTS: 1) the exosomes isolated from the ascites were membrane vesicles of about 30-90nm in diameter; 2) the exosomes expressed MHC class I molecules, HSP70, HSP90, Her2/Neu, and Mart1; and 3)umbilical cord blood-derived DCs previously exosome-primed stimulated resting T cells to differentiate and produce effective cytotoxicity. CONCLUSIONS: These results suggested that tumor-specific antigens present on exosomes can be presented by DCs derived from unrelated umbilical cord blood to induce tumor specific cytotoxicity and this may represent as a novel immunotherapy for ovarian cancer.

Lovgren, T. R., et al. (2002). "Enhanced in vitro and in vivo cytotoxicity of umbilical cord blood cells against human breast cancer following activation with IL-15 and colony stimulating factors." In Vivo **16**(6): 541-550.

BACKGROUND: Cord blood mononuclear cells (MNC) are a rich source of precursor cytotoxic effector cells. Earlier we have shown that interleukin-2 (IL-2)-activated MNC from cord blood have significant cytotoxic activity against human leukemia and breast cancer cells in vitro and in vivo, compared to MNC from peripheral blood. MATERIALS AND METHODS: In order to further improve the antitumor cytotoxic ability of cord blood MNC, IL-2 was combined with IL-15 and colony stimulating factors GMCSF, G-CSF and M-CSF for the activation. The activated cells were examined for their cytotoxic effects in vitro against human breast cancer cell lines MDA-231, MDA453 and SKB43 and in vivo against MDA-231 grown in SCID mice. Phenotypes of these activated cells were determined using flow cytometry. The expression of immune response related genes in activated cells was measured using RT-PCR techniques. RESULTS: There was a significant increase in cytotoxicity of the effector cells activated with IL-2, IL-15 and some colony stimulating factors compared to cells activated with each of these cytokines alone or other combinations. Our results demonstrated the increase in cytotoxicity appears to be due to: 1) increase in CD56-positive cytotoxic cells; 2) cytokine/cytotoxic factors produced by the effector cells, such as Interferon-7 and Perforin; 3) stimulation by accessory cells, such as dendritic cells. In vivo

administration of in vitro-activated cord blood cells into SCID mice bearing MDA-231 tumors reduced the number of metastases and increased survival compared to untreated tumor bearing controls. CONCLUSION: The combination of IL-2 with IL-15 and CSF is better for the activation of cord blood effector cells than to IL-2 alone.

Ma, G. L., et al. (2012). "[Study of inhibiting and killing effects of transgenic LIGHT human umbilical cord blood mesenchymal stem cells on stomach cancer]." Zhonghua Wei Chang Wai Ke Za Zhi **15**(11): 1178-1181.

OBJECTIVE: To study the inhibition and killing effect of transgenic LIGHT umbilical cord blood mesenchymal stem cells (UCBMSCs) on stomach carcinoma. METHODS: The LIGHT gene was recombined to construct the transfer plasmid pGC-FU-LIGHT by infusion technique. The 293T cells were co-transfected with the transfer plasmid pGC-FU-LIGHT, the construction plasmid Helper 1.0 and the envelope plasmid Helper 2.0 with the help of lipofectamine 2000 to produce lentiviral particles. Transgenic UCBMSCs (MSC-LIGHT) and empty carrier UCBMSCs (MSC) were obtained. Human gastric cancer cell SGC-7901 was injected into nude mice subcutaneously groin. The model of transplanted human gastric cancer cell SGC-7901 in nude mice was established. Tumorigenesis nude mice were separated into three groups randomly with 5 in each group: MSC-LIGHT group, MSC group, and NS group. Three groups of nude mice were injected around the tumor with MSC-LIGHT, MSC and NS every other day for 3 times. Four weeks later, the transplanted gastric cancer volume was measured. The expressions of LIGHT in the three groups were determined by RT-PCR and ELISA method. The necrosis area in the tumors was calculated under pathological examination. RESULTS: The average volume of transplanted tumor was (0.45+/-0.25) cm (3) in MSG-LIGHT group, (0.64+/-0.36) cm (3) in MSG group, and (1.21+/-0.79) cm (3) in NS group, and the difference was statistically significant ($P<0.05$). The LIGHT mRNA was 2.96+/-0.27, 1.23+/-0.47, and 0.73+/-0.10 respectively. The LIGHT protein was (167.89+/-2.31), (73.22+/-5.74), and (49.66+/-5.25) ng/L. The differences were all statistically significant among the three groups (both $P<0.01$). Pathological examination showed that the necrosis area was largest in MSC-LIGHT group. CONCLUSION: Transgenic UCBMSCs secret LIGHT in a paracrine manner, which has inhibition and killing effects on stomach carcinoma.

Markowicz, S., et al. (2006). "Nonviral transfection of human umbilical cord blood dendritic cells is feasible, but the yield of dendritic cells with transgene expression limits the application of this method in cancer immunotherapy." Acta Biochim Pol **53**(1): 203-212.

Dendritic cells (DC) generated from human umbilical cord blood might replace patients' DC in attempts to elicit tumor-specific immune response in cancer patients. We studied the efficiency of transfection of human cord blood DC with plasmid DNA carrying the enhanced version of green fluorescent protein (EGFP) as a reporter gene, to test if nonviral gene transfer would be a method to load DC with protein antigens for immunotherapy purposes. Cord blood mononuclear cells were cultured in serum-free medium in the presence of granulocyte-monocyte colony stimulating factor (GM-CSF), stem cell factor (SCF) and Flt-3 ligand (FL), to generate DC from their precursors, and thereafter transfected by electroporation. Maturation of DC was induced by stimulation with GM-CSF, SCF, FL and phorbol myristate acetate (PMA). Transfected DC strongly expressed EGFP, but transfection efficiency of DC, defined as HLA-DR (+) cells lacking lineage-specific markers, did not exceed 2.5%. Expression of the reporter gene was also demonstrated in the DC generated from transfected, purified CD34(+) cord blood cells, by stimulation with GM-CSF, SCF, FL, and tumor necrosis factor alpha (TNF-alpha). Transfection of CD34(+) cells was very efficient, but proliferation of the transfected cells was much reduced as compared to the untransfected cells. Therefore, the yield of transgene-expressing DC was relatively low. In conclusion, nonviral transfection of cord blood DC proved feasible, but considering the requirements for immunotherapy in cancer patients, transfection of differentiated DC or generation of DC from transfected hematopoietic stem cells provide only a limited number of DC expressing the transgene.

Qiu, L., et al. (2012). "Novel measurements of mammary stem cells in human umbilical cord blood as prospective predictors of breast cancer susceptibility in later life." Ann Oncol **23**(1): 245-250.

BACKGROUND: The size of the breast stem-cell pool could underlie the intrauterine roots of breast cancer. We studied whether breast stem cells exist in umbilical cord blood and if they correlate with hematopoietic stem-cell measurements that have been positively associated with perinatal risk factors for breast cancer. SUBJECTS AND METHODS: We isolated mononuclear cells from umbilical cord blood of 170 singleton full-term pregnancies and determined, by reverse transcription polymerase chain reaction, the presence of genes of putative breast epithelial stem-cell/progenitor markers [including epithelial cell adhesion molecule (EpCAM), CD49f (alpha6-integrin), CD117 (c-kit receptor), CD24, and CD29 (beta1-

integrin)]. By immunocytochemistry, we colocalized protein expressions of EpCAM+CD49f+, CD49f+CD24+, and CD24+CD29+. We correlated concentrations of putative breast stem-cell/progenitor subpopulations, quantified by flow cytometry, with concentrations of hematopoietic stem cells. RESULTS: Mammary stem-cell phenotypes were identified in umbilical cord blood. The measured EpCAM+ subpopulation was positively correlated with concentrations of CD34+ and CD34+CD38- hematopoietic stem cells (both P=0.006). Additionally, EpCAM+CD49f+ and CD49f+CD24+ subpopulations were positively correlated to the CD34+ cells (P=0.03 and 0.008, respectively). CONCLUSION: The positive association between measurable breast and hematopoietic stem cells in human umbilical cord blood suggests plausible mechanisms for a prenatal influence on breast cancer risk.

Qiu, L., et al. (2015). "Effect of preeclampsia on umbilical cord blood stem cells in relation to breast cancer susceptibility in the offspring." Carcinogenesis **36**(1): 94-98.

Women born from a preeclamptic (PE) pregnancy are associated with a lower risk of breast cancer. Prenatal and early-life exposures are hypothesized to influence breast cancer susceptibility through their effect on stem cells. We examined stem cell populations in umbilical cord blood from PE pregnancies and compared with those from pregnancies without this condition. We isolated mononuclear cells from 58 PE and 197 normotensive (non-PE) umbilical cord blood samples and examined the different stem cell populations. Hematopoietic (CD34(+) and CD34(+)CD38(-)), endothelial (CD34(+)CD133(+), CD34(+)VEGFR2(+), CD133(+)VEGFR2(+) and CD34(+)CD133(+)VEGFR2(+)), and putative breast (EpCAM (+), EpCAM (+)CD49f (+), EpCAM (+)CD49f (+)CD117(+), CD49f (+)CD24(+), CD24(+)CD29(+) and CD24(+)CD29(+)CD49f (+)) stem/progenitor cell subpopulations were quantified by flow cytometry and compared between PE and non-PE samples. Hematopoietic CD34(+) cell counts were significantly lowered in PE compared with non-PE samples (P = 0.039, Kruskal-Wallis test). Levels of CD34(+)CD133(+) endothelial progenitor cells were also lower in PE samples (P = 0.032, multiple regression analysis). EpCAM (+) and EpCAM (+)CD49f (+) putative breast stem cell levels were significantly lowered in PE subjects (multiple regression analysis: P = 0.038 and 0.007, respectively). Stratifying by newborn gender, EpCAM (+) and EpCAM (+)CD49f (+) stem cells were significantly lowered in PE samples of female, but not male, newborns. Umbilical cord blood samples from pregnancies complicated by preeclampsia thus had significantly lower levels of hematopoietic, endothelial, and putative breast stem cells than non-PE controls. With a lowered breast cancer risk for offspring of a PE pregnancy, our findings provide support to the hypothesis that susceptibility to breast oncogenesis may be affected by conditions and processes during the prenatal period.

Qiu, Y., et al. (2017). "Immunity Enhancement in Immunocompromised Gastrointestinal Cancer Patients with Allogeneic Umbilical Cord Blood Mononuclear Cell Transfusion." Biomed Res Int **2017**: 5945190.

Objectives. In order to enhance the immunity of cancer patients to prevent relapse or to prolong survival time, umbilical cord blood mononuclear cells (UCMCs) were transplanted to cancer patients. Patients and Methods. UCMCs were transfused to 63 immunocompromised gastrointestinal cancer patients with nonmyeloablative (NMA) conditioning regimen. Results. The clinical study showed that the number of both T and B cells increased much more rapidly after transfusion of UCMCs than that of the control group without transplantation ($p < 0.01$). Proinflammation cytokines IFNgamma and TNFalpha in serum increased to or above the normal range in 80.9% of patients at 12 weeks after UCMC transfusion. However, they recovered to the normal range in 21.7% of patients at the same time point in the control group only. In addition, the clinical investigation also showed that the transfusion of UCMC increased stable disease (SD) and reduced progressive disease (PD) significantly ($p < 0.01$); however, it did not have significant effects on complete response (CR), partial response (PR), or mortality rates compared with the control group ($p > 0.05$). Conclusions. UCMCs have powerful repairing effects on damaged cells and tissues and may reconstruct the impaired immunity. Transfusion of UCMCs could reconstruct the immunity of cancer patients with immunosuppression.

Roth, J. A., et al. (2014). "Design of a cost-effectiveness analysis alongside a randomized trial of transplantation using umbilical cord blood versus HLA-haploidentical related bone marrow in advanced hematologic cancer." J Comp Eff Res **3**(2): 135-144.

BACKGROUND: BMT CTN 1101 is a Phase III randomized controlled trial evaluating the comparative effectiveness of double unrelated umbilical cord blood (dUCB) versus HLA-haploidentical related donor bone marrow (haplo-BM) donor cell sources for blood or bone marrow transplantation (BMT) in patients with hematologic malignancies. Herein, we present the rationale, design and methods of the first cost-effectiveness analysis to be conducted alongside a BMT trial. METHODS: Consenting patients will provide health insurance information to allow

calculation of direct medical costs from reimbursement records, and will provide out-of-pocket costs, time costs and health-related quality of life measures through an online survey. These outcomes will inform a cost-effectiveness analysis comparing dUCB and haplo-BM donor cell sources from patient, payer and societal perspectives. CONCLUSION: Novel approaches may significantly change the cost, outcomes or availability of BMT. The results of this analysis will be the first to provide a comprehensive evaluation of the comparative effectiveness of these approaches from multiple perspectives.

Savarese, T. M., et al. (2007). "Correlation of umbilical cord blood hormones and growth factors with stem cell potential: implications for the prenatal origin of breast cancer hypothesis." Breast Cancer Res **9**(3): R29.

INTRODUCTION: Prenatal levels of mitogens may influence the lifetime breast cancer risk by driving stem cell proliferation and increasing the number of target cells, and thereby increasing the chance of mutation events that initiate oncogenesis. We examined in umbilical cord blood the correlation of potential breast epithelial mitogens, including hormones and growth factors, with hematopoietic stem cell concentrations serving as surrogates of overall stem cell potential. METHODS: We analyzed cord blood samples from 289 deliveries. Levels of hormones and growth factors were correlated with concentrations of stem cell and progenitor populations (CD34+ cells, CD34+CD38- cells, CD34+c-kit+ cells, and granulocyte-macrophage colony-forming units). Changes in stem cell concentration associated with each standard deviation change in mitogens and the associated 95% confidence intervals were calculated from multiple regression analysis. RESULTS: Cord blood plasma levels of insulin-like growth factor-1 (IGF-1) were strongly correlated with all the hematopoietic stem and progenitor concentrations examined (one standard-deviation increase in IGF-1 being associated with a 15-19% increase in stem/progenitor concentrations, all $P < 0.02$). Estriol and insulin-like growth factor binding protein-3 levels were positively and significantly correlated with some of these cell populations. Sex hormone-binding globulin levels were negatively correlated with these stem/progenitor pools. These relationships were stronger in Caucasians and Hispanics and were weaker or not present in Asian-Americans and African-Americans. CONCLUSION: Our data support the concept that in utero mitogens may drive the expansion of stem cell populations. The correlations with IGF-1 and estrogen are noteworthy, as both are crucial for mammary gland development.

Spanholtz, J., et al. (2010). "High log-scale expansion of functional human natural killer cells from umbilical cord blood CD34-positive cells for adoptive cancer immunotherapy." PLoS One **5**(2): e9221.

Immunotherapy based on natural killer (NK) cell infusions is a potential adjuvant treatment for many cancers. Such therapeutic application in humans requires large numbers of functional NK cells that have been selected and expanded using clinical grade protocols. We established an extremely efficient cytokine-based culture system for ex vivo expansion of NK cells from hematopoietic stem and progenitor cells from umbilical cord blood (UCB). Systematic refinement of this two-step system using a novel clinical grade medium resulted in a therapeutically applicable cell culture protocol. CD56(+)CD3(-) NK cell products could be routinely generated from freshly selected CD34(+) UCB cells with a mean expansion of >15,000 fold and a nearly 100% purity. Moreover, our protocol has the capacity to produce more than 3-log NK cell expansion from frozen CD34(+) UCB cells. These ex vivo-generated cell products contain NK cell subsets differentially expressing NKG2A and killer immunoglobulin-like receptors. Furthermore, UCB-derived CD56(+) NK cells generated by our protocol uniformly express high levels of activating NKG2D and natural cytotoxicity receptors. Functional analysis showed that these ex vivo-generated NK cells efficiently target myeloid leukemia and melanoma tumor cell lines, and mediate cytolysis of primary leukemia cells at low NK-target ratios. Our culture system exemplifies a major breakthrough in producing pure NK cell products from limited numbers of CD34(+) cells for cancer immunotherapy.

Strohsnitter, W. C., et al. (2008). "Correlation of umbilical cord blood haematopoietic stem and progenitor cell levels with birth weight: implications for a prenatal influence on cancer risk." Br J Cancer **98**(3): 660-663.

We examined the relation with birth weight and umbilical cord blood concentrations of haematopoietic stem and progenitor populations in 288 singleton infants. Across the whole range of birth weight, there was a positive relation between birth weight and CD34+CD38(-) cells, with each 500 g increase in birth weight being associated with a 15.5% higher (95% confidence interval: 1.6-31.3%) cell concentration. CD34+ and CD34+c-kit+ cells had J-shaped relations and CFU-GM cells had a U-shaped relation with birth weight. Among newborns with >or=3000 g birth weights, concentrations of these cells increased with birth weight, while those below 3000 g had higher stem cell concentrations than the reference category of 3000-3499 g. Adjustment for cord blood plasma insulin-like growth factor-1 levels weakened the stem and

progenitor cell-birth weight associations. The positive associations between birth weight and stem cell measurements for term newborns with a normal-to-high birth weight support the stem cell burden hypothesis of cancer risk.

Sun, B., et al. (2010). "Human umbilical cord blood mesenchymal stem cell-derived extracellular matrix prohibits metastatic cancer cell MDA-MB-231 proliferation." Cancer Lett **296**(2): 178-185.

It is not clear whether adult stem cell extracellular matrix (ECM) can regulate cancer cells. We demonstrated that the ECM produced by UCB-MSCs was able to arrest the growth of metastatic tumor cells by upregulating levels of PTEN in aggressive cancer cells. Human UCB-MSCs produced dickkopf (DKK1) are capable of inhibiting cancer cell proliferation but has no contribution to the tumor inhibition effect of UCB-MSC ECM. This study also provides an innovative approach to specifically examine the effect of stem cell microenvironments on cancer cells without the complexity of cell-cell interactions. In conclusion, human UCB-MSC ECM prohibits cancer cell proliferation.

Veluchamy, J. P., et al. (2017). "In Vivo Efficacy of Umbilical Cord Blood Stem Cell-Derived NK Cells in the Treatment of Metastatic Colorectal Cancer." Front Immunol **8**: 87.

Therapeutic monoclonal antibodies against the epidermal growth factor receptor (EGFR) act by inhibiting EGFR downstream signaling and by eliciting a natural killer (NK) cell-mediated antitumor response. The IgG1 mAb cetuximab has been used for treatment of RAS (wt) metastatic colorectal cancer (mCRC) patients, showing limited efficacy. In the present study, we address the potential of adoptive NK cell therapy to overcome these limitations investigating two allogeneic NK cell products, i.e., allogeneic activated peripheral blood NK cells (A-PBNK) and umbilical cord blood stem cell-derived NK cells (UCB-NK). While cetuximab monotherapy was not effective against EGFR (-) RAS (wt), EGFR (+) RAS (mut), and EGFR (+) BRAF (mut) cells, A-PBNK were able to initiate lysis of EGFR (+) colon cancer cells irrespective of RAS or BRAF status. Cytotoxic effects of A-PBNK (but not UCB-NK) were further potentiated significantly by coating EGFR (+) colon cancer cells with cetuximab. Of note, a significantly higher cytotoxicity was induced by UCB-NK in EGFR (-)RAS (wt) (42 +/- 8 versus 67 +/- 7%), EGFR (+) RAS (mut) (20 +/- 2 versus 37 +/- 6%), and EGFR (+) BRAF (mut) (23 +/- 3 versus 43 +/- 7%) colon cancer cells compared to A-PBNK and equaled the cytotoxic efficacy of the combination of A-PBNK and cetuximab. The antitumor efficacy of UCB-NK cells against cetuximab-resistant human EGFR (+) RAS (mut) colon cancer cells was further confirmed in an in vivo preclinical mouse model where UCB-NK showed enhanced antitumor cytotoxicity against colon cancer independent of EGFR and RAS status. As UCB-NK have been proven safe in a recently conducted phase I clinical trial in acute myeloid leukemia, a fast translation into clinical proof of concept for mCRC could be considered.

Xu, C., et al. (2018). "Umbilical Cord Blood-Derived Natural Killer Cells Combined with Bevacizumab for Colorectal Cancer Treatment." Hum Gene Ther.

Colorectal cancer (CRC) is among the cancers with the highest incidence globally, and it currently ranks as the fourth leading cause of cancer-related deaths worldwide. Novel strategies for the treatment of advanced CRC are urgently needed, and adoptive transfer of allogeneic natural killer (NK) cells represents an attractive option. In this study, we successfully expanded NK cells from umbilical cord blood (UCB) with membrane-bound interleukin (IL)-21, termed eUCB-NK cells. eUCB-NK cells efficiently lysed CRC cell lines in vitro and secreted significantly higher levels of interferon-gamma, tumor necrosis factor-alpha, granulocyte-macrophage colony stimulating factor, and chemokine ligand 3 compared with IL-2-stimulated NK cells. Adoptive transfer of these NK cells significantly inhibited the growth of HT29 xenografts, whereas LoVo tumors were not effectively controlled with eUCB-NK cells. Higher numbers of NK cells inside HT29 tumors, not seen in LoVo tumors, might contribute to the differences in response to eUCB-NK cells. Bevacizumab increased extravasation of adoptively transferred NK cells into LoVo tumors and improved the therapeutic activity of eUCB-NK cells. These results justify clinical translation of UCB-derived NK cell-based therapeutics, used alone or in combination with bevacizumab, as a novel treatment option for patients with CRC.

Zhu, X., et al. (2013). "Gene therapy of gastric cancer using LIGHT-secreting human umbilical cord blood-derived mesenchymal stem cells." Gastric Cancer **16**(2): 155-166.

BACKGROUND: Mesenchymal stem cells (MSCs) have the ability to migrate into tumors and therefore are potential vehicles for the therapy of malignant diseases. In this study, we investigated the use of umbilical cord blood mesenchymal stem cells (UCB-MSCs) as carriers for a constant source of transgenic LIGHT (TNFSF14) to target tumor cells in vivo. METHODS: Lentiviral vectors carrying LIGHT genes were constructed, producing viral particles with a titer of 2 x 10(8) TU/L. Fourteen days after UCB-

MSCs transfected by LIGHT gene packaged lentivirus had been injected into mouse gastric cancer models, the expression levels of LIGHT mRNA and protein were detected by reverse transcription polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA). Then the tumors' approximate volumes were measured. RESULTS: The treatment with MSC-LIGHT demonstrated a strong suppressive effect on tumor growth compared to treatment with MSC and NaCl ($p < 0.001$). Examination of pathological sections of the tumor tissues showed that the areas of tumor necrocis in the MSC-LIGHT group were larger than those in the MSC group. Moreover, we found that MSCs with LIGHT were able to significantly induce apoptosis of tumor cells. The expression levels of LIGHT mRNA and protein were significantly higher in the UCB-MSCs with the LIGHT gene than the levels in UCB-MSCs ($p < 0.001$). CONCLUSION: These results suggest that UCB-MSCs carrying the LIGHT gene have the potential to be used as effective delivery vehicles in the treatment of gastric cancers.

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