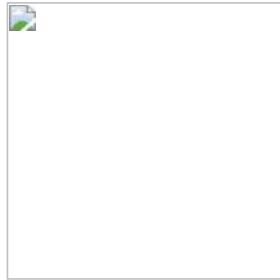


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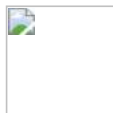
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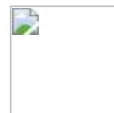
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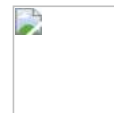
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# **Anti-cancer Potency and Mechanism of Human Umbilical Cord Blood Stem Cell**

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## **Abstract**

Human umbilical cord blood (hUCB) as a useful source of stem cell, has been kept in the stem cell bank and serves as a useful source as the last treatment option for a severe illness in the future. In regards to immunogenicity, it has been reported that hUCBSC has a low expression of HLA class I and II. In general, stem cell mechanism is not only through the incorporation of stem cell into the tissue, but stem cell can also secrete factors that can affect the surrounding cells.

hUCBSC can induce apoptosis in cervical and lung cancer cells. hUCBSC can inhibit growth of leukemic, cervical cancer and glioma cells. In addition, hUCBSC can inhibit invasion of glioma and lung cancer cells. Most of the reports showed that hUCBSC transplants are aimed for hematologic malignancies. There were low rates of malignant relapse after hUCBSC transplantation, suggesting that for patients at high relapse risk, hUCBSC could be the better option. hUCBSC showed as a good source for both dendritic and NK cells. Due to its high potency, hUCBSC should be developed further for treatment of breast and other type of cancers.

**Keywords:** cord blood stem cell, cancer, immunogenicity, HLA, NK cell, dendritic cell

## **Introduction**

Human umbilical cord blood (hUCB) as a useful source of stem cell, can be collected immediately after parturition. hUCB stem cell (hUCBSC) has been kept in the stem cell bank (Wijaya, 2007) and serves as a useful source as the last treatment option for a severe illness in the future (Sandra F, 2008). In regards to immunogenicity, it has been reported that hUCBSC has a low expression of HLA class I and II (Sardjono, 2010). Therefore the umbilical cord blood stem cell is a potential choice for allogeneic treatment, although partially human leukocyte antigen (HLA) mismatched (Sachdeva, 2018).

hUCBSC has been widely studied for the regenerative purposes, but it also known that hUCBSC homes to not just injured tissues but also tumors (Halim, 2010). hUCBSC can be affected and in the same time, hUCBSC can also affect the tumor cells. In general, stem cell mechanism is not only through the incorporation of stem cell into the tissue, but stem cell can also secrete factors that can affect the surrounding cells (Sandra, 2017a). The secreted factors also known as secretome. In secretome, a broad panel of proteins including growth factors, chemokines and cytokines can be found.

## **Effect of hUCBSC on Cancer Cell**

A study on leukemic cells showed that hUCB mesenchymal stem cells (MSC) inhibited proliferation of HL60 and K562 cells without inducing apoptosis. Growth inhibition was shown at the G0/G1 cell cycle. The p38 mitogen-activated protein kinase (MAPK) is important for the growth inhibitory effect of hUCB-MSC on HL60 and K562 cells (Tian, 2010).



In cervical cancer, secretome derived from conditioned media (CM) of hUCB mesenchymal stem cell (MSC) significantly induced apoptosis of HeLa cervical cancer cells in a concentration and time dependent manner through mitochondrial apoptotic pathway (Sandra, 2014). In addition, CM-hUCB-MSC secretome might inhibit HeLa cells growth as well. The MSC, can be derived from various tissues, such as bone marrow (Lubis, 2011), umbilical cord blood, Wharton jelly (Chouw, 2017, Widowati, 2018), adipose tissue (Sardjono, 2009; Widowati, 2012), dental pulp and periodontal ligament (Feter, 2017; Sandra, 2017), is one of potential stem cell types to be used for allogeneic treatment (Moenadjat, 2013). MSC has been reported potential for allogenic treatment, since it has lack expression of human leucocyte antigen (HLA) class II (Aini, 2008).

Meanwhile in glioma cells, hUCBSC has been reported to play a role in controlling glioma cell cycle progression and invasion. hUCBSC was shown to regulate U251 and 5310 cells progression at the G0-G1 level by downregulating extracellular signal regulated kinase (ERK), c-Myc, cyclin D1, cyclin-dependent kinase (CDK) 4 and CDK 6 (Velpula 2011, Velpula, 2012). In addition, hUCBSC induced expression of Myc associated factor X (Max) dimerization protein (Mad) 1, that competitively bound to Max to repress the c-Myc/Max-mediated gene transcription (Velpula, 2012). Therefore hUCBSC could regulate the expression of glioma cell cycle and ERK-associated invasion.

For lung cancer, the effects of hUCB-MSC on H1299 cells invasion and proliferation were evaluated using a Matrigel-based Transwell assay and Cell Counting Kit-8 assay, respectively. Results showed that the hUCB-MSC significantly inhibited invasion and induced apoptosis of H1299 lung cancer cells. The hUCB-MSC significantly suppressed AKT, phosphoinositide 3-kinase (PI3K), signal

transducer and activator of transcription (STAT) 3 and mammalian target of rapamycin (mTOR) (Chai, 2018).

Based on these 3 studies, several conclusions can be made. hUCBSC can induce apoptosis in cervical and lung cancer cells. hUCBSC can inhibit growth of leukemic, cervical cancer and glioma cells. In addition, hUCBSC can inhibit invasion of glioma and lung cancer cells. Potency of hUCBSC in other cancer cells should be explored further.

### **hUCBSC-derived Dendritic and NK Cell**

Targeted therapy based on monoclonal antibody (mAb) has been developed for the treatment of cancers. However, some of the mAbs have limited efficacy and need additional or other treatments. For example, in Ras wild type (WT) colorectal cancer, treatment of IgG1 mAb cetuximab has been reported to have limited efficacy. Meanwhile, there are potential therapy based on specific cells, namely dendritic and natural killer (NK) cells.

hUCBSC-derived dendritic cell has been reported to have the ability to induce stronger antigen-specific immunity and more potent anti-tumor effects than peripheral blood mononuclear cell (PBMNC)-derived dendritic cells. The surface markers expression of hUCBSC-derived dendritic cells was higher than those of PBMNC-derived dendritic cells. The hUCBSC-derived dendritic cells had better antigen-presentation abilities, induced higher numbers of interferon (IFN)- $\gamma$ -secreting antigen-specific CD8<sup>+</sup> T-cells, and stimulated more potent antigen-specific cytotoxic T-cell (CTL) activities. In addition, hUCBSC-derived dendritic cells had higher expression of ERK and phosphorylated Akt, and lower expression of phosphorylated p38, than PBMC-derived dendritic cells (Chang, 2012).

hUCBSC-derived NK cell induced a significantly higher cytotoxicity in epidermal growth factor receptor (EGFR)-Ras WT, EGFR-RASmut, and EGFR-BRAFmut colon cancer cells compared to activated peripheral blood-derived NK (a-PBNK) cells and equaled the cytotoxic efficacy of the combination of a-PBNK cells and IgG1 mAb cetuximab (Veluchamy, 2017). Large volume hUCBSC-derived NK cell production under good manufacturing practice (GMP) has been established in a fully closed, large-scale, cell culture bioprocess. The cryopreserved CD34<sup>+</sup> hUCBSC can be expanded 2,000 fold and differentiated into CD56<sup>+</sup> CD3<sup>-</sup> NK cell (Spanholtz, 2011).

hUCBSC showed as a good source for both dendritic and NK cells. Therefore, both hUCBSC-derived dendritic and NK cells could be a potential modalities to treat cancer. The hUCBSC-derived dendritic and NK cells could be suitable to diminish particular cancer cells.

### **hUCBSC Treatment and Clinical Trial**

Most of the reports showed that hUCBSC transplants are aimed for hematologic malignancies. hUCBSC has been acquired as a standard practice in pediatrics, and nowadays hUCBSC has been expanded to be practiced in adults as well. hUCBSC has been used for treatment of acute leukemia in children and adults, chronic myeloid leukemia, myelodysplastic syndrome and lymphoid malignancies (Brunstein, 2011). There were low rates of malignant relapse after hUCBSC transplantation, suggesting that for patients at high relapse risk, hUCBSC could be the better option. In addition, hUCBSC transplantation has lower rates of chronic graft versus host disease (GvHD) when compared with PBSC transplant (Dahlberg, 2017).

hUCBSC-derived NK cell has been reported for treatment of acute myeloid

leukemia (AML). Patients received  $3-30 \times 10^6/\text{kg}$  body weight hUCBSC-derived NK cells after lymphodepleting chemotherapy (Dolstra, 2017). This study suggested hUCBSC-derived NK cells as a promising, potential "off-the-shelf" translational immunotherapy for AML.

hUCBSC transplants for breast cancer patient has been reported. Patients received a median of  $9.9 \times 10^6$  expanded and unexpanded nucleated cells per kilogram body weight (Shpall, 2002). The study suggested that the CD34 selection and *ex vivo* expansion of hUCBSC prior to transplantation of hUCBSC was feasible. Another study in metastatic breast cancer has been reported as well. An *ex vivo* expansion system for hUCBSC, in which CD34<sup>+</sup> hUCBSCs were cultured. The patient received  $1.83 \times 10^7/\text{kg}$  of total nucleated hUCBSCs and  $7.7 \times 10^4/\text{kg}$  of CD34<sup>+</sup> expanded and unexpanded hUCBSCs. Results showed that there was not acute adverse effects after infusion of the cultured hUCBSCs (Oki, 2004).

## **Conclusion**

hUCBSC can induce apoptosis and inhibit growth cancer cells. In addition, hUCBSC can also inhibit invasion of cancer cells. hUCBSC can be a good source for both dendritic and NK cells, so that it can be "off-the-shelf" translational immunotherapy for AML. hUCBSC has been used for treatment of hematologic malignancies in children and adults. For patients at high relapse risk, hUCBSC could be the better option. Due to hUCBSC lack expression of HLA, despite hematologic malignancies, hUCBSC treatment should be develop further for breast and other type of cancers.

## References

1. Aini, N., Setiawan, B., and Sandra, F., "Karakteristik Biologis dan Diferensiasi Stem Cell: Fokus pada Mesenchymal Stem Cell," *CDK*. **35**, 64-67 (2008).
2. Brunstein, C.G., "Umbilical cord blood transplantation for the treatment of hematologic malignancies," *Cancer Control* **18**, 222-236 (2011).
3. Chai, L., Bai, L., Li, L., Chen, F., and Zhang, J., "Biological functions of lung cancer cells are suppressed in co-culture with mesenchymal stem cells isolated from umbilical cord," *Exp. Therapeut. Med.* **15**, 1076-1080 (2018).
4. Chang, M.C., Lee, C.N., Chen, Y.L., Chiang, Y.C., Sun, W.Z., Hu, Y.H., et al., "Cord blood stem-cell-derived dendritic cells generate potent antigen-specific immune responses and anti-tumour effects," *Clin. Sci. (Lond)*. **123**, 347-360 (2012).
5. Chouw, A., Dirgantara, Y., Putera, B.W., Sartika, C.R., Meutia, D., Yuliana, P., and Sandra, F., "Proliferation and Characterization of Wharton-jelly's Derived Mesenchymal Stromal Cell Using Plasma Rich Platelet and Plasma Platelet Lysate," *Cytotherapy* **19**, S152 (2017).
6. Dahlberg, A., and Milano, F., "Cord blood transplantation: rewind to fast forward," *Bone Marrow Transplant*. **52**, 799-802 (2017).
7. Dolstra, H., Roeven, M.W.H., Spanholtz, J., Hangalapura, B.N., Tordoir, M., Maas, F., et al., "Successful Transfer of Umbilical Cord Blood CD34<sup>+</sup> Hematopoietic Stem and Progenitor-derived NK Cells in Older Acute Myeloid Leukemia Patients," *Clin. Cancer Res.* **23**, 4107-4118 (2017).
8. Feter, Y., Afiana, N.S., Chandra, J.N., Abdullah, K., Shafira, J., and Sandra, F., "Dental Mesenchymal Stem Cell: Its Role in Tooth Development, Types, Surface Antigens and Differentiation Potential," *Mol. Cell. Biomed. Sci.* **1**, 50-57 (2017).

9. Halim, D., Murti, H., Sandra, F., Boediono, A., Djuwantono, T., and Setiawan, B., *Stem Cell: Dasar Teori & Aplikasi Klinis* (Erlangga, Jakarta, Indonesia, 2010).
10. Lubis, A.M., Sandhow, L., Lubis, V.K., Noor, A., Gumay, F., Merlina, M., *et al.*, "Isolation and Cultivation of Mesenchymal Stem Cells from Iliac Crest Bone Marrow for Further Cartilage Defect Management," *Acta Med. Indones.* **43**, 178-84 (2011).
11. Moenadjat, Y., Merlina, M., Surjadi, C.F., Sardjono, C.T., Kusnadi, Y., and Sandra, F., "The application of human umbilical cord blood mononuclear cells in the management of deep partial thickness burn," *Med. J. Indones.* **22**, 92-99 (2013).
12. Oki, M., Ando, K., Nakajima, H., Nakano, Y., Itagaki, H., Nakashioya, C., *et al.*, "Cord blood transplantation supported with ex vivo expanded fraction for a patient with myelodysplastic syndrome and metastatic breast cancer," *Rinsho Ketsueki.* **45**, 1048-1052 (2004).
13. Sachdeva, A., Gunasekaran, V., Malhotra, P., Bhurani, D., Yadav, S.P., Radhakrishnan, N., *et al.*, "Umbilical Cord Blood Banking: Consensus Statement of the Indian Academy of Pediatrics," *Indian Pediatr.* **55**, 489-494 (2018).
14. Sandra, F., Murti, H., Aini, N., Sardjono, C., and Setiawan, B., "Potensi Terapi Sel Punca dalam Dunia Kedokteran dan Permasalahannya," *JKM* **8**, 94-101 (2008).
15. Sandra, F., Sudiono, J., Sidharta, E.A., Sunata, E.P., Sungkono, D.J., Dirgantara, Y., *et al.*, "Conditioned Media of Human Umbilical Cord Blood Mesenchymal Stem Cell-derived Secretome Induced Apoptosis and Inhibited Growth of HeLa Cells," *Indones. Biomed. J.* **6**, 57-62 (2014).

16. Sandra, F., Sudiono, J., Binartha, C.T.O., Chouw, A., Djamil, M.S., "Growth and Osteogenic Differentiation of CD117+ Dental Pulp and Periodontal Ligament Cells," *Indones. Biomed. J.* **9**, 78-83 (2017).
17. Sandra, F. and Lahirin, R., "Human Umbilical Cord Blood Serum Has Higher Potential in Inducing Proliferation of Fibroblast than Fetal Bovine Serum," *Mol. Cell. Biomed. Sci.* **1**, 65-69 (2017).
18. Sardjono, C.T., Setiawan, M., Frisca, Saputra, V., Aniko, G., and Sandra, F., "Application of A Modified Method for Stem Cell Isolation from Lipoaspirates in A Basic Lab," *Med. J. Indones.* **18**, 91-96 (2009).
19. Sardjono, C.T., Setiawan, M., Suyatna, F.D., Japutri, I., Setiawan, B., and Sandra, F., "Immunogenicity Characterization of Mononucleated Cells Originated from Umbilical Cord Blood," *Med. J. Indones.* **19**, 14-20 (2010).
20. Shpall, E.J., Quinones, R., Giller, R., Zeng, C., Baron, A.E., Jones, R.B., et al., "Transplantation of ex vivo expanded cord blood," *Biol. Blood Marrow Transplant.* **8**, 368-376 (2002).
21. Spanholtz, J., Preijers, F., Tordoir, M., Trilsbeek, C., Paardekooper, J., de Witte T., et al., "Clinical-grade generation of active NK cells from cord blood hematopoietic progenitor cells for immunotherapy using a closed-system culture process," *PLoS One* **6**, e20740 (2011).
22. Tian, K., Yang, S., Ren, Q., Han, Z., Lu, S., Ma, F., et al., "p38 MAPK contributes to the growth inhibition of leukemic tumor cells mediated by human umbilical cord mesenchymal stem cells," *Cell Physiol. Biochem.* **26**, 799-808 (2010).
23. Velpula, K.K., Dasari, V.R., Tsung, A.J., Dinh, D.H., Rao, J.S., "Transcriptional repression of Mad-Max complex by human umbilical cord blood stem cells

- downregulates extracellular signal-regulated kinase in glioblastoma," *Stem Cells Dev.* **21**, 1779-1793 (2012).
24. Velpula, K.K., Dasari, V.R., Tsung, A.J., Gondi, C.S., Klopfenstein, J.D., Mohanam, S., et al., "Regulation of glioblastoma progression by cord blood stem cells is mediated by downregulation of cyclin D1," *PLoS One* **6**, e18017 (2011).
25. Veluchamy, J.P., Lopez-Lastra, S., Spanholtz, J., Bohme, F., Kok, N., Heideman, D.A., et al., "In Vivo Efficacy of Umbilical Cord Blood Stem Cell-Derived NK Cells in the Treatment of Metastatic Colorectal Cancer," *Front Immunol.* **8**, 87 (2017).
26. Widowati, W., Sardjono, C.T., Wijaya, L., Laksmiawati, D.R., and Sandra, F., "Extract of *Curcuma longa* L. and (-)-Epigallo Catechin-3-Gallate Enhanced Proliferation of Adipose Tissue-derived Mesenchymal Stem Cells (AD-MSCs) and Differentiation of AD-MSCs into Endothelial Progenitor Cells," *J. USA China Med. Sci.* **9**, 22-29 (2012).
27. Widowati, W., Afifah, E., Mozef, T., Sandra, F., Rizal, R., Amalia, A., et al., "Effects of insulin-like growth factor-induced Wharton jelly mesenchymal stem cells toward chondrogenesis in an osteoarthritis model," *Iran J Basic Med Sci.* **21**, 745-752 (2018).
28. Wijaya, M.T. and Sandra, F., "Proses dalam Umbilical Cord Blood Banking," *CDK.* **34**, 217-220 (2007).





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## BioMIC2018 Prosiding AIP: Mohon Final Proof dan Penandatanganan TCA

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# Anti-cancer Potency and Mechanism of Human Umbilical Cord Blood Stem Cell

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**Abstract.** Human umbilical cord blood (hUCB) as a useful source of stem cell, has been kept in the stem cell bank and serves as a useful source as the last treatment option for severe illness in the future. In regards to immunogenicity, it has been reported that hUCBSC has low expression of HLA class I and II. In general, stem cell mechanism is not only through the incorporation of stem cell into the tissue, but stem cell can also secrete factors that can affect the surrounding cells. hUCBSC can induce apoptosis in cervical and lung cancer cells. hUCBSC can inhibit the growth of leukemic, cervical cancer and glioma cells. In addition, hUCBSC can inhibit invasion of glioma and lung cancer cells. Most of the reports showed that hUCBSC transplants are aimed for hematologic malignancies. There were low rates of malignant relapse after hUCBSC transplantation, suggesting that for patients at high relapse risk, hUCBSC could be the better option. hUCBSC showed as a good source for both dendritic and NK cells. Due to its high potency, hUCBSC should be developed further for the treatment of breast and other types of cancers.

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## INTRODUCTION

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## HUCBSC TREATMENT AND CLINICAL TRIAL

Most of the reports showed that hUCBSC transplants are aimed for hematologic malignancies. hUCBSC has been acquired as a standard practice in pediatrics, and nowadays hUCBSC has been expanded to be practiced in adults as well. hUCBSC has been used for the treatment of acute leukemia in children and adults, chronic myeloid leukemia, myelodysplastic syndrome and lymphoid malignancies [24]. There were low rates of malignant relapse after hUCBSC transplantation, suggesting that for patients at high relapse risk, hUCBSC could be the better option. In addition, hUCBSC transplantation has lower rates of chronic graft versus host disease (GvHD) when compared with PBSC transplant [25]. hUCBSC-derived NK cell has been reported for treatment of acute myeloid leukemia (AML). Patients received  $3 \times 10^6$  per kg body weight to  $30 \times 10^6$  per kg body weight hUCBSC-derived NK cells

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after lymphodepleting chemotherapy [26]. This study suggested hUCBSC-derived NK cells as a promising, potential "off-the-shelf" translational immunotherapy for AML.

hUCBSC transplants for breast cancer patient has been reported. Patients received a median of  $9.9 \times 10^6$  expanded and unexpanded nucleated cells per kg body weight [27]. The study suggested that the CD34 selection and *ex vivo* expansion of hUCBSC prior to transplantation of hUCBSC was feasible. Another study in metastatic breast cancer has been reported as well. An *ex vivo* expansion system for hUCBSC, in which CD34<sup>+</sup> hUCBSCs were cultured. The patient received  $1.83 \times 10^7$  per kg of total nucleated hUCBSCs and  $7.7 \times 10^4$  per kg of CD34<sup>+</sup> expanded and unexpanded hUCBSCs. Results showed that there were not acute adverse effects after infusion of the cultured hUCBSCs [28].

## CONCLUSION

hUCBSC can induce apoptosis and inhibit the growth of cancer cells. In addition, hUCBSC can also inhibit the invasion of cancer cells. hUCBSC can be a good source for both dendritic and NK cells so that it can be "off-the-shelf" translational immunotherapy for AML. hUCBSC has been used for the treatment of hematologic malignancies in children and adults. For patients at high relapse risk, hUCBSC could be the better option. Due to hUCBSC lack expression of HLA, despite hematologic malignancies, hUCBSC treatment should be developed further for breast and other types of cancers.

## REFERENCES

1. M. T. Wijaya and F. Sandra, CDK. **34**(157), 217–220 (2007). [Bahasa Indonesia].
2. F. Sandra, H. Murti, N. Aini, C. Sardjono, and B. Setiawan, JKM **8**(1), 94–101 (2008). [Bahasa Indonesia].
3. C. T. Sardjono, M. Setiawan, F. D. Suyatna, I. Japutri, B. Setiawan, and F. Sandra, Med. J. Indones. **19**(1), 14–20 (2010).
4. A. Sachdeva, V. Gunasekaran, P. Malhotra, D. Bhurani, S. P. Yadav, N. Radhakrishnan, M. Kalra, *et al.*, Indian Pediatr. **55**(6), 489–494 (2018).
5. D. Halim, H. Murti, F. Sandra, A. Boediono, T. Djuwantono, and B. Setiawan, *Stem Cell: Dasar Teori dan Aplikasi Klinis* [Stem Cell: Basic Theory & Clinical Applications] (Erlangga, Jakarta, Indonesia, 2010). [Bahasa Indonesia].
6. F. Sandra, J. Sudiono, C. T. O. Binartha, A. Chouw, and M. S. Djamil, Indones. Biomed. J. **9**(2), 78–83 (2017).
7. K. Tian, S. Yang, Q. Ren, Z. Han, S. Lu, F. Ma, L. Zhang, *et al.*, Cell Physiol. Biochem. **26**, 799–808 (2010).
8. F. Sandra, J. Sudiono, E. A. Sidharta, E. P. Sunata, D. J. Sungkono, Y. Dirgantara, and A. Chouw, Indones. Biomed. J. **6**(1), 57–62 (2014).
9. A. M. Lubis, L. Sandhow, V. K. Lubis, A. Noor, F. Gumay, M. Merlina, W. Yang, *et al.*, Acta Med. Indones. **43**(3), 178–184 (2011).
10. A. Chouw, Y. Dirgantara, B. W. Putera, C. R. Sartika, D. Meutia, P. Yuliana, and F. Sandra, Cytotherapy **19**(5), S152 (2017).
11. W. Widowati, E. Afifah, T. Mozef, F. Sandra, R. Rizal, A. Amalia, Y. Arinta, *et al.*, Iran J. Basic. Med. Sci. **21**(7), 745–752 (2018).
12. C. T. Sardjono, M. Setiawan, Frisca, V. Saputra, G. Aniko, and F. Sandra, Med. J. Indones. **18**, 91–96 (2009).
13. W. Widowati, C. T. Sardjono, L. Wijaya, D. R. Laksmiawati, and F. Sandra, J. USA China Med. Sci. **9**, 22–29 (2012).
14. Y. Feter, N. S. Afiana, J. N. Chandra, K. Abdullah, J. Shafira, and F. Sandra, Mol. Cell. Biomed. Sci. **1**, 50–57 (2017).
15. F. Sandra and R. Lahirin, Mol. Cell. Biomed. Sci. **1**, 65–69 (2017).
16. Y. Moenadjat, M. Merlina, C. F. Surjadi, C. T. Sardjono, Y. Kusnadi, and F. Sandra, Med. J. Indones. **22**, 92–99 (2013).
17. N. Aini, B. Setiawan, and F. Sandra, CDK. **35**, 64–67 (2008). [Bahasa Indonesia].
18. K. K. Velpula, V. R. Dasari, A. J. Tsung, C. S. Gondi, J. D. Klopfenstein, S. Mohanam, and J. S. Rao, PLoS One **6**(3), 1–13 (2011).
19. K. K. Velpula, V. R. Dasari, A. J. Tsung, D. H. Dinh, and J. S. Rao, Stem Cells Dev. **21**, 1779–1793 (2012).
20. L. Chai, L. Bai, L. Li, F. Chen, and J. Zhang, Exp. Therapeut. Med. **15**, 1076–1080 (2018).

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21. M. C. Chang, C. N. Lee, Y. L. Chen, Y. C. Chiang, W. Z. Sun, Y. H. Hu, C. A. Chen, *et al.*, *Clin. Sci. (Lond)*. **123**(6), 347–360 (2012).
22. J. P. Veluchamy, S. Lopez-Lastra, J. Spanholtz, F. Bohme, N. Kok, D. A. Heideman, H. M. Verheul, *et al.*, *Front. Immunol.* **8**(87), 1–11 (2017).
23. J. Spanholtz, F. Preijers, M. Tordoir, C. Trilsbeek, J. Paardekooper, T. de Witte, N. Scaap, *et al.*, *PLoS One* **6**, e20740 (2011).
24. C. G. Brunstein, *Cancer Control* **18**, 222–236 (2011).
25. A. Dahlberg and F. Milano, *Bone Marrow Transplant.* **52**, 799–802 (2017).
26. H. Dolstra, M. W. H. Roeven, J. Spanholtz, B. N. Hangalapura, M. Tordoir, F. Maas, M. Leenders, *et al.*, *Clin. Cancer Res.* **23**(15), 4107–4118 (2017).
27. E. J. Shpall, R. Quinones, R. Giller, C. Zeng, A. E. Baron, R. B. Jones, S. I. Bearman, *et al.*, *Biol. Blood Marrow Transplant.* **8**, 368–376 (2002).
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hUCBSC showed as a good source for both dendritic and NK cells. Therefore, both hUCBSC-derived dendritic and NK cells could be a potential modality to treat cancer. The hUCBSC-derived dendritic and NK cells could be suitable to diminish particular cancer cells.

## HUCBSC TREATMENT AND CLINICAL TRIAL

Most of the reports showed that hUCBSC transplants are aimed for hematologic malignancies. hUCBSC has been acquired as a standard practice in pediatrics, and nowadays hUCBSC has been expanded to be practiced in adults as well. hUCBSC has been used for the treatment of acute leukemia in children and adults, chronic myeloid leukemia, myelodysplastic syndrome and lymphoid malignancies [24]. There were low rates of malignant relapse after hUCBSC transplantation, suggesting that for patients at high relapse risk, hUCBSC could be the better option. In addition, hUCBSC transplantation has lower rates of chronic graft versus host disease (GvHD) when compared with PBSC transplant [25]. hUCBSC-derived NK cell has been reported for treatment of acute myeloid leukemia (AML). Patients received  $3 \times 10^6$  per kg body weight to  $30 \times 10^6$  per kg body weight hUCBSC-derived NK cells

**Commented [WU1]:** Satuan dari angka  $3 \times 10^6$  itu apa ya? Cells? atau bagaimana?  
Apakah benar seperti ini?

**Commented [aa2]:** Kalau dibaca sampai selesai, maka dapat diketahui bahwa satuannya adalah *cell*, tepatnya adalah: *hUCBSC-derived NK cells*. Jadi ini sudah benar.

after lymphodepleting chemotherapy [26]. This study suggested hUCBSC-derived NK cells as a promising, potential "off-the-shelf" translational immunotherapy for AML.

hUCBSC transplants for breast cancer patient has been reported. Patients received a median of  $9.9 \times 10^6$  expanded and unexpanded nucleated cells per kg body weight [27]. The study suggested that the CD34 selection and *ex vivo* expansion of hUCBSC prior to transplantation of hUCBSC was feasible. Another study in metastatic breast cancer has been reported as well. An *ex vivo* expansion system for hUCBSC, in which CD34<sup>+</sup> hUCBSCs were cultured. The patient received  $1.83 \times 10^7$  per kg of total nucleated hUCBSCs and  $7.7 \times 10^4$  per kg of CD34<sup>+</sup> expanded and unexpanded hUCBSCs. Results showed that there were not acute adverse effects after infusion of the cultured hUCBSCs [28].

## CONCLUSION

hUCBSC can induce apoptosis and inhibit the growth of cancer cells. In addition, hUCBSC can also inhibit the invasion of cancer cells. hUCBSC can be a good source for both dendritic and NK cells so that it can be "off-the-shelf" translational immunotherapy for AML. hUCBSC has been used for the treatment of hematologic malignancies in children and adults. For patients at high relapse risk, hUCBSC could be the better option. Due to hUCBSC lack expression of HLA, despite hematologic malignancies, hUCBSC treatment should be developed further for breast and other types of cancers.

## REFERENCES

1. M. T. Wijaya and F. Sandra, CDK. **34**(157), 217–220 (2007). [Bahasa Indonesia].
2. F. Sandra, H. Murti, N. Aini, C. Sardjono, and B. Setiawan, JKM **8**(1), 94–101 (2008). [Bahasa Indonesia].
3. C. T. Sardjono, M. Setiawan, F. D. Suyatna, I. Japutri, B. Setiawan, and F. Sandra, Med. J. Indones. **19**(1), 14–20 (2010).
4. A. Sachdeva, V. Gunasekaran, P. Malhotra, D. Bhurani, S. P. Yadav, N. Radhakrishnan, M. Kalra, *et al.*, Indian Pediatr. **55**(6), 489–494 (2018).
5. D. Halim, H. Murti, F. Sandra, A. Boediono, T. Djuwanton, and B. Setiawan, *Stem Cell: Dasar Teori dan Aplikasi Klinis* [Stem Cell: Basic Theory & Clinical Applications] (Erlangga, Jakarta, Indonesia, 2010). [Bahasa Indonesia].
6. F. Sandra, J. Sudiono, C. T. O. Binartha, A. Chouw, and M. S. Djamil, Indones. Biomed. J. **9**(2), 78–83 (2017).
7. K. Tian, S. Yang, Q. Ren, Z. Han, S. Lu, F. Ma, L. Zhang, *et al.*, Cell Physiol. Biochem. **26**, 799–808 (2010).
8. F. Sandra, J. Sudiono, E. A. Sidharta, E. P. Sunata, D. J. Sungkono, Y. Dirgantara, and A. Chouw, Indones. Biomed. J. **6**(1), 57–62 (2014).
9. A. M. Lubis, L. Sandhow, V. K. Lubis, A. Noor, F. Gumay, M. Merlina, W. Yang, *et al.*, Acta Med. Indones. **43**(3), 178–184 (2011).
10. A. Chouw, Y. Dirgantara, B. W. Putera, C. R. Sartika, D. Meutia, P. Yuliana, and F. Sandra, Cytotherapy **19**(5), S152 (2017).
11. W. Widowati, E. Afifah, T. Mozef, F. Sandra, R. Rizal, A. Amalia, Y. Arinta, *et al.*, Iran J. Basic. Med. Sci. **21**(7), 745–752 (2018).
12. C. T. Sardjono, M. Setiawan, Frisca, V. Saputra, G. Aniko, and F. Sandra, Med. J. Indones. **18**, 91–96 (2009).
13. W. Widowati, C. T. Sardjono, L. Wijaya, D. R. Laksmiawati, and F. Sandra, J. USA China Med. Sci. **9**, 22–29 (2012).
14. Y. Feter, N. S. Afiana, J. N. Chandra, K. Abdullah, J. Shafira, and F. Sandra, Mol. Cell. Biomed. Sci. **1**, 50–57 (2017).
15. F. Sandra and R. Lahirin, Mol. Cell. Biomed. Sci. **1**, 65–69 (2017).
16. Y. Moenadjat, M. Merlina, C. F. Surjadi, C. T. Sardjono, Y. Kusnadi, and F. Sandra, Med. J. Indones. **22**, 92–99 (2013).
17. N. Aini, B. Setiawan, and F. Sandra, CDK. **35**, 64–67 (2008). [Bahasa Indonesia].
18. K. K. Velpula, V. R. Dasari, A. J. Tsung, C. S. Gondi, J. D. Klopfenstein, S. Mohanam, and J. S. Rao, PLoS One **6**(3), 1–13 (2011).
19. K. K. Velpula, V. R. Dasari, A. J. Tsung, D. H. Dinh, and J. S. Rao, Stem Cells Dev. **21**, 1779–1793 (2012).
20. L. Chai, L. Bai, L. Li, F. Chen, and J. Zhang, Exp. Therapeut. Med. **15**, 1076–1080 (2018).

Commented [WU3]: Satuannya dari angka ini apa ya?

Commented [aa4]: Yang ini juga demikian, jadi kalau dibaca sampai selesai akan ketahuan bahwa ini adalah *cell*, tepatnya adalah: *expanded and unexpanded nucleated cells*. Jadi ini sudah benar.

Commented [WU5]: Halaman berapa?

Commented [aa6]: Yang dikutip adalah 1 buku, bukan per-chapter ataupun per halaman.

21. M. C. Chang, C. N. Lee, Y. L. Chen, Y. C. Chiang, W. Z. Sun, Y. H. Hu, C. A. Chen, *et al.*, *Clin. Sci. (Lond)*. **123**(6), 347–360 (2012).
22. J. P. Veluchamy, S. Lopez-Lastra, J. Spanholtz, F. Bohme, N. Kok, D. A. Heideman, H. M. Verheul, *et al.*, *Front. Immunol.* **8**(87), 1–11 (2017).
23. J. Spanholtz, F. Preijers, M. Tordoir, C. Trilsbeek, J. Paardekooper, T. de Witte, N. Scaap, *et al.*, *PLoS One* **6**, e20740 (2011).
24. C. G. Brunstein, *Cancer Control* **18**, 222–236 (2011).
25. A. Dahlberg and F. Milano, *Bone Marrow Transplant.* **52**, 799–802 (2017).
26. H. Dolstra, M. W. H. Roeven, J. Spanholtz, B. N. Hangalapura, M. Tordoir, F. Maas, M. Leenders, *et al.*, *Clin. Cancer Res.* **23**(15), 4107–4118 (2017).
27. E. J. Shpall, R. Quinones, R. Giller, C. Zeng, A. E. Baron, R. B. Jones, S. I. Bearman, *et al.*, *Biol. Blood Marrow Transplant.* **8**, 368–376 (2002).
28. M. Oki, K. Ando, H. Nakajima, Y. Nakano, H. Itagaki, C. S. Nakashioya, Kato, *et al.*, *Rinsho Ketsueki* **45**(9), 1048–1052 (2004).



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