

# Hematopoietic Progenitor Cell (HPC) Analysis – Literature Review –

Nina GAMPERLING\*<sup>1</sup> and Torsten REINECKE\*<sup>2</sup>

\*<sup>1</sup> Sysmex Corporation of America, One Wildlife Way, Long Grove, IL 60047-9596, USA.

\*<sup>2</sup> Scientific Department, Sysmex Europe GmbH, Tarpen 15a, 22419 Hamburg, Germany.

(Sysmex J Int 11 : 77-80, 2001)

**Key Words** Hematopoietic Progenitor Cell, CD34<sup>+</sup> Cells, SE-Series

The most primitive of all blood cells is the hematopoietic progenitor cell (HPC) that is capable of dividing and differentiating into the specific blood cell type required by the body. Researchers since the 1970s have been working on methods to collect, isolate, concentrate and store enough circulating peripheral blood stem cells (PBSCs) for restoring hematopoietic function following bone marrow ablative therapy (chemotherapy or radiation). Hematopoietic progenitor cells can be harvested from bone marrow as well as umbilical cord blood and G-CSF mobilized peripheral blood. In order to obtain an adequate amount of cells, it is necessary to approximate the number of peripheral blood stem cells harvested after mobilization utilizing results obtained from peripheral blood specimens. It is also important to determine whether umbilical cord bloods have sufficient progenitor cells before proceeding with an expensive banking process. Several methods have been used to determine

cord blood progenitor content as well as the optimal time of harvest. These laboratory methods include CD34<sup>+</sup> cell counts based on the flow cytometric method, colony-forming units (CFU), and total nucleated cell count (TNC). As early as 1995, it was reported that the IMI channel on the SE instrument could be used to approximate the number of these HPC. Since then, several investigators have examined the use of the HPC parameter on the SE for assessing HPC potential in a product. At this time, the HPC parameter on the Sysmex instrument is for investigational use only and is not cleared by the FDA for market in the United States of America.

This brief report should give a review of the application of HPC analysis, by the different methods. A selection of publications from international scientific journals have been collected and listed according to method and relevant key words. Please find these key words and respective reference numbers in **Table 1** below.

**Table 1** HPC Analysis by key words

Key Words	Article reference numbers
Sysmex HPC Method	13, 14, 15, 16, 22, 25, 27, 34, 40, 41, 42, 44, 46, 47, 50, 51, 52, 53, 57, 68, 69, 70, 74, 75, 76, 78, 79, 80, 82, 84, 85
CD34 <sup>+</sup> Method	2, 4, 6, 7, 10, 12, 23, 24, 31, 49, 58, 59, 60, 62, 63, 64, 66, 67, 71, 77
CD34 Negative	1, 11, 35, 54, 65, 83
Total Nucleated Count (TNC)	5, 27, 33, 39, 71, 84, 85
Colony-Forming Unit	8, 28, 32, 48, 56, 61, 64, 71
Hematopoietic Stem Cell – General Information	30, 43, 55, 65, 73, 81
Regulatory Guidelines	9, 17, 18, 19, 20, 21, 36, 37, 38
R-Series Instrument Method	27, 45
Bone Marrow Transplant	3, 72
Umbilical Cord Engraftment/Transplant	26, 29

## HPC Literature List

- 1) Bhatia M, et al.: A newly discovered class of human hematopoietic cells with SCID-repopulating activity. *Nature Medicine*, 4 (9), 1998.
- 2) Brecher ME, et al.: North american multicenter study on flow cytometric enumeration of CD34<sup>+</sup> hematopoietic stem cells. *Journal of Hematotherapy*, 5: 227-236, 1996.
- 3) Buckner C Dean: Autologous bone marrow transplants to hematopoietic stem cell support with peripheral blood stem cells: A historical perspective. *Journal of Hematotherapy*, 8: 233-236, 1999.
- 4) Chang A, Ma DDF: The influence of flow cytometric gating strategy on the standardization of CD34<sup>+</sup> cell quantitation: an Australian multicenter study. *Journal of Hematotherapy*, 5: 605-616, 1996.
- 5) Chervenick PA, Boggs, DR: *In vitro* growth of granulocytic and mononuclear cell colonies from blood of normal individuals. *Blood*, 37 (2): February, 1971.
- 6) Chin-Yee I, et al.: Quality assurance of stem cell enumeration by flow cytometry. *Cytometry*, 30: 296-303, 1997.
- 7) D'Arena, G, et al.: Circulating CD34<sup>+</sup> absolute cell number is the best single parameter to predict the quality of leukapheresis yield. *Bone Marrow Transplant*, 22 (2): 215-216, July, 1998.
- 8) Debelack-Fehir KM, et al.: Hemopoietic colony forming units in fresh and cryopreserved peripheral blood cells of canines and man. *Experimental Hematology*, 3 (2): 109-116, 1975.
- 9) Food and Drug Administration (FDA): Guidance for premarket notification for automated differential cell counters for immature or abnormal blood cells; Final guidance for industry and FDA. Document issued on: December 4, 2001. CDRH. FDA.
- 10) Fontão-Wendel R, et al.: The absolute number of circulating CD34<sup>+</sup> cells as the best predictor of peripheral hematopoietic stem cell yield. *Journal of Hematotherapy*, 8: 255-262, 1999.
- 11) Goodell MA: CD34<sup>+</sup> or CD34<sup>-</sup>: Does it really matter? *Blood*, 94 (8): 2545-2547, October, 1999.
- 12) Gratama JW, et al.: Analysis of variation in results of CD34<sup>+</sup> hematopoietic progenitor cell enumeration in a multicenter study. *Cytometry (Communications in Clinical Cytometry)*, 30: 109-117, 1997.
- 13) Gutenshon K, et al.: Monitoring the timing of the peripheral blood stem cell apheresis : Application of the hematopoietic progenitor cell analysis. *Infusion Therapy and Transfusion Medicine*, 28: 271-276, 2001; and presented at *European Sysmex Symposium. January 25-26, 2001.*
- 14) Houwen B, et al.: Human progenitor cell (HPC) identification in patients undergoing stem cell mobilization, using a routine hematology analyzer (poster). *Laboratory Hematology*, 3 (2): 166 (a), 1997.
- 15) Houwen B, et al.: Screening for hematopoietic stem cells by the Sysmex SE-9000 hematology analyzer (poster). *Laboratory Hematology*, 3 (2): 184 (b), 1997 and *European Symposium 1997.*
- 16) Houwen B, et al.: The timing of peripheral blood stem cell harvests: screening for hematopoietic stem cells on the SE-9000 (abstract). *Laboratory Hematology*, 2 (1): 51, 1996.
- 17) International Council for Standardization in Haematology (ICSH): Guidelines for the evaluation of blood cell analyzers including those used for differential leucocytes and reticulocyte counting and cell marker applications. *Clinical Laboratory Haematology*, 16: 157-174, 1994.
- 18) International Council for Standardization in Haematology (ICSH): Recommendations of the international council for standardization in haematology for ethylenediaminetetraacetic acid anticoagulation of blood for blood cell counting and sizing. *American Journal of Clinical Pathology*, 100 (4): 371-372, 1993.
- 19) International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and International Council for Standardization in Haematology (ICSH): Approved recommendation (1986) on the theory of reference values. Part 1. The concept of reference values. *Journal of Clinical Chemistry and Clinical Biochemistry*, 25: 337-342, 1987.
- 20) International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and International Council for Standardization in Haematology (ICSH): Approved recommendation (1987) on the theory of reference values. Part 5. Statistical treatment of collected reference values. Determination of reference limits. *Journal of Clinical Chemistry and Clinical Biochemistry*, 25: 645-656, 1987.
- 21) International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and International Council for Standardization in Haematology (ICSH): Approved recommendation (1987) on the theory of reference values. Part 6. Presentation of observed values related to reference values. *Journal of Clinical Chemistry and Clinical Biochemistry*, 25: 657-662, 1987.
- 22) Ishii T, et al.: SE-9000 IMI channel- Focusing on the roles and functions of surfactant. *Sysmex Journal International*, 7 (2): 123-128, 1997.
- 23) Johnsen HE and Knudsen LM: Nordic flow cytometry standards for CD34<sup>+</sup> cell enumeration in blood leukapheresis products : Report from the second Nordic workshop. *Journal of Hematotherapy*, 5: 237-245, 1996.
- 24) Knudsen LM, et al.: Evaluation of mobilized CD34<sup>+</sup> cell counts to guide timing and yield of large-scale collection by leukapheresis. *Journal of Hematotherapy*, 7: 45-52, 1998.
- 25) Kraai R, et al.: Hematopoietic stem and precursor cell analysis in umbilical cord blood using the Sysmex SE-9000 IMI channel. *Cytometry*, 46 (2): 114-118, April, 2001.
- 26) Laughlin MJ, et al.: Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *New England Journal of Medicine*, 344 (24), June 14, 2001.

- 27) Lebeck LL, et al.: Peripheral blood stem cell harvests: Laboratory indicators for the timing of apheresis procedures (abstract of presentation). *Laboratory Hematology*, 1, 1: 62, 1996.
- 28) Lewis ID, et al.: Standardization of the CFU-GM assay using hematopoietic growth factors. *Journal of Hematotherapy*, 5: 625-630, 1996.
- 29) Lim FT, et al.: The number of nucleated cells reflects the hematopoietic content of umbilical cord blood for transplantation. *Bone Marrow Transplant*, 24 (9): 965-970, November 1999.
- 30) Lord BI, Dexter TM: Which are the hematopoietic stem cells? (or: Don't debunk history!). *Experimental Hematology*, 23: 1237-1241, 1995.
- 31) Luider J, et al.: Factors influencing yields of progenitor cells for allogeneic transplantation: Optimization of G-CSF dose, day of collection, and duration of leukapheresis. *Journal of Hematotherapy*, 6: 575-580, December 1997.
- 32) McCredie KB, et al.: Cells capable of colony formation in the peripheral blood of man. *Science*, 171: 293-294, January 1971.
- 33) Miyovic A, et al.: Blast counts in blood progenitor cell (BPC) correlate with CD34<sup>+</sup> cells and CFU-GM and are a useful predictor of haemopoietic recovery after autologous BPC transplantation collections. *Bone Marrow Transplantation*, 21: 869-872, 1998.
- 34) Mougi H, et al.: Determination of peripheral blood stem cells using automated hematology analyzer, SE-9000 IMI channel. *Sysmex Journal International*, 7 (2): 63-70, 1997.
- 35) Nakauchi H: Hematopoietic stem cells: Are they CD34-positive or CD34-negative? *Nature Medicine*, 4 (9):1009-1010, 1998.
- 36) National Committee for Clinical Laboratory Standards (NCCLS): *How to define and determine reference intervals in the clinical laboratory; Approved Guideline—Second Edition*, NCCLS document C28-A2, (ISBN P56238-269-I), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 2000.
- 37) National Committee for Clinical Laboratory Standards (NCCLS): *Preliminary evaluation of quantitative clinical laboratory methods; Approved Guideline*, NCCLS document EP 10-A, (ISBN 1-56238-348-5), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 10987-1898, 1998.
- 38) National Committee for Clinical Laboratory Standards (NCCLS): *Procedures for the collection of diagnostic blood specimens by skin puncture; Approved Standard—Fourth Edition*, NCCLS document H4-A4, (ISBN 1-56238-111-9), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1999.
- 39) Oertel J, et al.: Detection of small numbers of immature cells in the blood of healthy subjects. *Journal of Clinical Pathology*, 51 (12): 886-890, December 1998.
- 40) Oliver DA, et al.: Comparison of hematopoietic progenitor cell (HPC) parameter as measured by Sysmex 9500 with CD34 and CFU assays for the purpose of rapid assessment of circulating progenitors. (abstract) at The American Society of Hematology (ASH) Meeting, 1998.
- 41) Oliver DA, et al.: Correlation of hematopoietic progenitor cell parameter as measured by Sysmex 9500 with CD34 and colony forming unit assays on cord blood-implications for banking. (abstract) at International Society for Hematotherapy and Graft Engineering (ISHAGE), Oslo, Norway, May/June, 1999.
- 42) Oliver DA, et al.: Rapid and inexpensive screening of hematopoietic precursors using the Sysmex SE-9500. Draft publication.
- 43) Pelehach L: The story of the stem cell. *Laboratory Medicine*, 27 (9): 588-599, September 1996.
- 44) Pollard Y, et al.: An adequate CD34<sup>+</sup> cell apheresis yield is unlikely with low Sysmex SE-9500 haemopoietic progenitor cell (HPC) blood counts (presentation) at International Society of Laboratory Hematologists (ISLH), Banff, Canada, 1998 and (abstract) at ISLH, Kobe, Japan, 1999.
- 45) Pollard Y, et al.: Automated reticulocyte analysis with RNA quantification by the Sysmex R-1000 to monitor peripheral blood stem cell transplantation. *Sysmex Journal International*, 4 (1): 83-87, 1994.
- 46) Pollard Y, et al.: Use of the haemopoietic progenitor cell count of the Sysmex SE-9500 to refine apheresis timing of peripheral blood stem cells. *British Journal of Haematology*, 106: 538-544, 1999.
- 47) Product Development Division, TOA Medical Electronics: The outline of stem cell monitor program. *Sysmex Journal International*, 7 (2): 82-88, 1997.
- 48) Ragab AH, et al.: The culture of colony forming units from the peripheral blood and bone marrow of children with acute lymphocytic leukemia. *Cancer*, 34 (3): 663-9, September 1974.
- 49) Remes K, et al.: Daily measurements of blood CD34<sup>+</sup> cells after stem cell mobilization predict stem cell yield and posttransplant hematopoietic recovery. *Journal of Hematotherapy*, 6: 13-19, 1997.
- 50) Saigo K, et al.: Application of the stem cell monitor program for harvesting peripheral blood stem cells. *Sysmex Journal International*, 9 (2): 151-159, 1999.
- 51) Saigo K, et al.: Detection of hematopoietic stem cells by flow cytometry, hematology analyzer or in vitro culture method. Abstract only. *Jpn J Clin Pathol, Suppl 110: 124-130, May 1999.*
- 52) Saigo K, et al.: Optimum timing of peripheral blood stem cell harvest using SE-9000 IMI channel -in the cases of patients with breast cancer-. *Sysmex Journal International*, 7 (2): 71-81, 1997.
- 53) Sasaki H, et al.: Screening test for hematopoietic stem cells in umbilical cord blood by automated hematology analyzer, SE-9000. Abstract only. *Jpn J Clin Pathol, Suppl 110 : 131-133, May 1999.*
- 54) Sato T, et al.: Reversible expression of CD34 by murine hematopoietic stem cells. *Blood*, 94 (8): 2548-2554, October 1999.
- 55) Schultze W: The importance of hemopoietic stem cells in the treatment of hemo-oncological disease. *Sysmex*

*Journal International*, 7 (2): 53-56, 1998.

- 56) Eaves C, and Lambie K: Atlas of Human Hematopoietic Colonies. Stem Cell Technologies Inc. 1995.
- 57) Endoh A, et al.: Hematopoietic progenitor cell counts performed by the Sysmex SE-9000 analyzer can guide timing of peripheral blood stem cell harvest. *Anticancer*, 21: 601-604, 2001.
- 58) Serke S, et al.: Analysis of CD34-expressing cells in clinical practice. *Vox Sanguinis* 74, Suppl 2: 469-475, 1998.
- 59) Serke S, et al.: Analysis of CD34-positive hemopoietic progenitor cells from normal human adult peripheral blood; flow-cytometrical studies and *in-vitro* colony (CFU-GM, BFU-E) assays. *Annals of Hematology*, 62 :45-53, 1991.
- 60) Serke S, et al.: European survey of the flow cytometric determination of CD34-expressing cells. *Cytotherapy*, 1 (4): 343-347, 1999.
- 61) Serke S, et al.: Imprecision of counting CFU-GM colonies and CD34-expressing cells. *Bone Marrow Transplantation*, 20: 57-61, 1997.
- 62) Serke S, et al.: *In-vitro* clonogenicity of mobilized peripheral blood CD34-expressing cells: inverse correlation to both relative and absolute numbers of CD34-expressing cells. *British Journal of Haematology*, 95: 234-240, 1996.
- 63) Serke S, et al.: Multiparameter flow-cytometrical quantitation of circulating CD34<sup>+</sup> cells: correlation to the quantitation of circulating haemopoietic progenitor cells by *in vitro* colony-assay. *British Journal of Haematology*, 77: 453-459, 1991.
- 64) Siena S, et al.: Flow cytometry for clinical estimation of circulating hematopoietic progenitors for autologous transplantation in cancer patients. *Blood*, 77(2) :400-409, January 1991.
- 65) Spangrude GJ and Cooper DD: Paradigm shifts in stem-cell biology. *Seminars in Hematology*, 37 (1), Suppl 2: 3-10, January 2000.
- 66) Sutherland DR, and Keating A: The CD34 antigen: structure, biology, and potential clinical applications. *Journal of Hematotherapy*, 1: 115-129, 1992.
- 67) Sutherland DR, et al.: The ISHAGE guidelines for CD34<sup>+</sup> cell determination by flow cytometry. *Journal of Hematotherapy*, 5: 213-226, 1996.
- 68) Takekawa K, et al.: Determination of hematopoietic stem cells in peripheral blood by an automated hematology analyzer (SE-9000). *Acta Haematologica*, 100: 130-136, 1998.
- 69) Takekawa K, et al.: Identification of hematopoietic stem cells by the SE-9000 automated hematology analyzer in peripheral blood stem cell harvest samples (abstract). *Blood*, 88 (10): 250b, Suppl 1 (Part 2 of 2), 1996.
- 70) Takekawa K, et al.: Identification of hematopoietic stem cells by the SE-9000 automated hematology analyzer in peripheral blood stem cell harvest samples. *Acta Haematologica*, 98: 54-55, 1997.
- 71) Tao M, et al.: Comparison of peripheral blood CD34<sup>+</sup> concentration, colony-forming units granulocyte-macrophage and mononuclear cells in leukapheresed product for the prediction of peripheral blood CD34<sup>+</sup> cell yield harvest. *Annals Academy of Medicine Singapore*, 26 (3): 308-311, May 1997.
- 72) Thomas ED: Bone marrow transplantation: Past, present and future. *Haematologica*, 76: 352-356, 1991.
- 73) To LB, et al.: The biology and clinical uses of blood stem cells. *Blood*, 89 (7): 2233-2258, 1997.
- 74) Wall DA, et al.: Use of the hematopoietic progenitor cell (HPC) parameter of the Sysmex SE-9500 to monitor stem cell pheresis. Abstract at The American Society of Hematology (ASH), December 1999.
- 75) Wall DA, and Oliver DA: Use of the hematopoietic progenitor cell parameter on the Sysmex SE-9500 as a screening tool for circulating hematopoietic precursors in pediatrics. *Infusion Therapy and Transfusion Medicine*, 28: 271-276, 2001.
- 76) Wang F, et al.: Screening for hematopoietic stem cells by the Sysmex SE-9500 hematology analyzer. Draft publication.
- 77) Watts MJ: Clinical relevance of CD34<sup>+</sup> cell measurements in PBSC transplantation. *Cytotherapy*, 1 (4): 348-350, 1999.
- 78) Yamane T, et al.: Determination of hematopoietic stem cells in peripheral blood by automated hematology analyzer, SE-9000. *Sysmex Journal International*, 7 (2): 57-62, 1997.
- 79) Yamane T, et al.: Possibility of identification of hematopoietic stem cells using a conventional blood cell counter. *European Journal of Haematology*, 55: 207-208, 1995.
- 80) Yamane T, et al.: Simple method for determination of hematopoietic stem cells. Abstract only. *Jpn J Clin Pathol*, 46 (4): 367-371, April, 1998.
- 81) Yin AH, et al.: AC133, a novel marker for human hematopoietic stem and progenitor cells. *Blood*, 90 (12): 5002-5012, December, 1997.
- 82) Yu J, et al.: Enumeration of HPC in mobilized peripheral blood with the Sysmex SE-9500 predicts final CD34<sup>+</sup> cell yield in the apheresis collection. *Bone Marrow Transplantation*, 25: 1157-1164, 2000.
- 83) Zanjani E, et al.: Human bone marrow CD34<sup>-</sup> cells engraft *in vivo* and undergo multilineage expression that includes giving rise to CD34<sup>+</sup> cell. *Experimental Hematology*, 26: 353-360, 1998.
- 84) Zini G, et al.: Stem cell PBSC screening for transplantation in the routine hematology laboratory. (abstract) *Laboratory Hematology*, 3 (2): 185, 1997.
- 85) Zini G, et al.: Stem cell screening for transplantation in the routine hematology laboratory. (abstract) *Laboratory Hematology*, 3 (2): 166, 1997.