EXPRESSION OF THE STEM CELL FACTOR RECEPTOR C-KIT (CD117) IN ACUTE LEUKEMIAS

Christian Sperling,* Stefan Schwartz,° Thomas Büchner,# Eckhard Thiel,°
Wolf-Dieter Ludwig*

Dept. of Hematology, Oncology and Tumor Immunology, Robert-Rössle-Klinik, Humboldt-Universität, Berlin; °Dept. of Hematology and Oncology, Universitätsklinikum Benjamin Franklin, Freie Universität Berlin; #Dept. of Internal Medicine, Universität Münster; Germany

ABSTRACT

Background and Objective. The receptor for stem cell factor (CD117) is the gene product of the c-kit proto-ontogene. Together with its ligand, the stem cell factor (SCF), it plays an important role in hematopoiesis. In this study, we review the cellular distribution of CD117 in normal hematopoiesis and in hematopoietic malignancies focusing on the differential expression in subtypes of acute leukemias.

Evidence and Information Sources. This review is based on a literature search in the Medline database, personal publications and results obtained as a reference laboratory of the German AML-BFM, AMLCG and ALL multi-center therapy studies.

State of the Art and Perspectives. Membrane expression of CD117 can be found on leukemic blasts from approximately 60% of adult and childhood AML patients, often associated with an immature immunophenotype (CD34+). Moreover, AML with t(8;21) are frequently CD117 positive. Despite earlier reports, most recent studies have not been able to demonstrate any significant prognostic impact of CD117 expression in either childhood or adult AML. A small proportion of T-lineage ALL (9%), mainly consisting of immature pro-T/pre-T-ALL, is CD117 positive. CD117 expression is rare in B-cell-precursor-ALL and occurs in less than 3% of cases. CD117 in combination with other antigens might facilitate the immunologic characterization of acute leukemias, especially those of myeloid and early T-cell origin.
©1997, Ferrata Storti Foundation

The stem cell factor receptor (SCFR, CD117) is encoded by the c-*kit* proto-oncogene, which is the cellular counterpart of the v-*kit* oncogene of a transforming feline retrovirus (HZ4-feline sarcoma virus). It is a 145kD transmembrane glycoprotein which is homologous to several other growth factor receptors such as the receptors for macrophage colony stimulating factor (M-CSF, CSF-1, c-*fms*), platelet-derived growth factor α and β (PDGF-Rα, PDGF-Rβ), and the newly described growth factor receptor STK-1, which is the human homologue of the murine FLK2/FLT3 receptor.[1] These receptors are members of the class III receptor tyrosine kinase (RTK) family (reviewed in ref. #2), and are characterized by an extracellular ligand binding-region of five immunoglobulin-like domains, a hydrophobic transmembrane domain and a cytoplasmic domain with tyrosine kinase activity split by an insert.[3] The human gene for the c-*kit* receptor is in a region in the long arm of chromosome 4 (4q11- 4q13).[4,5] Ligand binding induces formation of receptor homodimers, activation of tyrosine kinase and phosphorylation of several intracellular targets including autophosphorylation followed by activation of a signal transduction cascade. In addition to its expression in normal hematopoiesis, c-*kit* has been found on AML blasts, as well as myeloid, erythroid, megakaryocytic and lymphoid cell lines.[6-8] Non-hematopoietic cells expressing c-*kit* include normal tissues such as epithelial cells of the breast, parotid and dermal sweat glands, melanocytes, central nervous system (particularly in the cerebellum, the hippocampus, and the dorsal horn of the spinal cord), placenta, interstitial cells of the testes and ovaries,[9,10] as well as tissues from small cell lung cancer,[11-13] breast cancer[14] or melanoma,[15] and cell lines derived from the respective tumors.[16]

The biology of c-*kit* and its ligand has been recently reviewed.[17,18] In this study, we briefly sum-

marize c-*kit* expression in normal hematopoiesis and focus on the differential expression in hematologic malignancies, as well as its clinical and presumed prognostic implications in acute leukemias.

C-kit expression in hematopoietic cells

The cellular distribution of CD117 expression has been investigated at the mRNA and protein level with a variety of techniques, including polymerase chain reaction, Northern Blot, and flow cytometric analysis. The monoclonal antibodies (moAbs) YB5.B8,[19,20] SR-1,[21] 17F11,[22] and MTK1[23] have been applied to detect c-*kit* expression on the cell-surface membrane of various subpopulations of bone marrow cells. These moAbs recognize different epitopes of the c-*kit* receptor, and vary in their ability of inhibiting SCF action and intrinsic agonist activities.[24] Using the moAb YB5.B8, expression of CD117 has been demonstrated in approximately 2-5% of normal bone marrow cells.[25] Up to 60-70% of CD34+ bone-marrow progenitor cells co-express CD117,[8,26,27] and the CD34+/CD117+ fraction contains the majority of clonogenic cells (CFU-GM [granulocyte/macrophage colony-forming unit], CFU-mix and BFU-E [burst-forming unit-erythroid]).[27] Although in general, expression of CD117 during hematopoietic development is highest at the early stages and then continuously diminishes with maturation, the most primitive hematopoietic progenitors may express lesser amounts of c-*kit* than progenitors committed to the granulocyte/macrophage lineage.[28] A considerable proportion of CD34+/CD117+ cells in normal bone marrow coexpress CD33, thus representing committed myeloid progenitors.[26] Soluble SCF has a limited effect on several *in vitro* systems, but acts synergistically with GM-CSF, G-CSF, IL-3, IL-6 or erythropoietin in promoting proliferation and differentiation of hematopoietic stem cells and early myeloid progenitors.[29,30] Membrane-bound SCF on stromal cells may be involved in adhesion mechanisms between hematopoietic progenitors and bone marrow stroma.[31]

Besides their effect on the myeloid lineage, c-*kit* and its ligand are also involved in early antigen-independent B-cell development, though c-*kit* might not be indispensable for B-cell ontogenesis.[32-36] A small proportion of CD34+ immature bone marrow cells co-express c-*kit* and the B cell marker CD19.[26,27] SCF synergizes with IL-7 in promoting proliferation of murine pre-B cells,[37-39] and anti-c-*kit* antibody suppresses the growth of B-cell precursors *in vitro*.[32] Thymic stromal cells contain mRNA for SCF, whereas both thymocytes and thymic stroma express c-*kit*, thus indicating that SCF/SCFR might also play a role in early T-cell development.[40] A subset of triple negative thymocytes (CD3− CD4− CD8−) expresses the c-*kit* receptor that is functional in these cells.[8,41]

C-kit expression in hematopoietic malignancies

Reflecting its distribution in normal hematopoiesis, the highest frequency of CD117 expression is found in early myeloid neoplasias, i.e. acute myeloid leukemia (AML) and clonal stem cell disorders, such as myeloproliferative disorders (MPS) and myelodysplastic syndromes (MDS). In these malignancies, an increased CD117 expression has been found on peripheral blood mononuclear cells and bone marrow, as compared with normal controls. The highest percentages of CD117-positive cells were observed in the advanced stages of the disease, i.e. acceleration/myeloid blast crisis in MPS and RAEB/RAEB-t in MDS, respectively.[42,43] Once regarded as a specific marker for AML,[44] it was discovered that CD117 is also expressed in a small proportion of acute lymphoblastic leukemias (ALL) which is consistent with its putative role in early stages of B- and T-cell development. In malignant lymphomas, c-*kit* expression seems to be restricted to CD30+ anaplastic large cell lymphomas and Hodgkin's disease,[45] while Burkitt's lymphomas,[46] other high grade lymphomas or mature lymphoid neoplasias lack CD117 expression. Malignant cells from multiple myeloma seem to express the c-*kit* antigen, while normal plasma cells do not.[47]

C-kit expression in acute myeloid leukemia

The cell surface antigen encoded by the c-*kit* proto-oncogene was first identified in a subgroup of AML by using a moAb against AML blast cells.[19] This finding was confirmed by many subsequent studies, indicating that c-*kit* expression can be found on the protein or at least on the mRNA level in the majority of AMLs. Depending on the method employed, CD117 surface expression could be demonstrated in blasts of approximately 50-70% (range from 29% to 89%) of all AML cases[22,23,43,44,48-56] with the quantitative level of receptor expression in individual cases being highly variable, and generally similar to or less than that found in normal stem and progenitor cells.[57]

Expression of CD117 has been detected in all morphological subtypes of AML (see Table 1), while most of the studies published so far have not found a clear correlation with FAB-subtypes.[21,44,48,56,58,59] Using antibody YB5.B8, the frequency of c-*kit* positivity seemed to be higher in the FAB M0/M1/M2 subtypes as compared with M5,[50,60] although a higher incidence of c-*kit* expression was observed in M4 and M5 AML when a different antibody (SR-1) was applied.[54] Interestingly, a significant proportion of promyelocytic leukemia expresses CD117.[61]

The role of CD117 expression in defining more immature leukemias is still a matter of controversy. Our own data, obtained in 429 adult and 173 childhood consecutive AML cases, did not disclose a significant correlation between CD117 expression

Table 1. CD117 expression in 423 adult AML patients according to morphological subtype.

	CD117 positive	
FAB type	n	%
M0	33/47	70.2
M1	57/83	68.7
M2	105/124	84.7
M3	11/16	68.7
M4	50/102	49.0
M5	4/30	11.7
M6	14/16	87.5
M7	1/1	–
Total	275/423	65.0

Table 2. CD117 expression in 218 adult ALL patients.

	CD117 positive	
ALL subtype	n	%
B-cell precursor ALL	0/115	0.0
T-lineage-ALL	9/103	8.7
Pro T-ALL	5/21	23.8
T-ALL	4/82	4.9
myAG+ T-ALL	8/42	19.0
myAg- T-ALL	1/60	1.6

myAG: CD13, CD33, CD65s.

and immature M0/M1-subtypes, although an association of CD34 expression and CD117 positivity was found.[60] These results, which represent the largest study in investigating CD117 expression by flow cytometry in blast cells from AML patients using monoclonal antibody YB5.B8 with a direct immunofluorescence technique as previously described,[62] are in accordance with other recent reports studying smaller groups of patients (Table 2).[42-44,50,52]

CD7 is also often expressed in CD117-positive AML,[61] on the other hand, CD14, CD15, CD64 and CD4 were rarely found (ref. #60 and unpublished results).

There is little data on cytogenetic features of c-kit-positive AML. In our series of 233 adult AML patients, chromosomal aberrations were more frequent in CD117 positive AML than in CD117 negative AML (41% vs. 60%, $p < 0.05$).[60] In addition, we found CD117 expression in 10/10 AML cases with the t(8;21) aberration.

Previous studies regarding the prognostic significance of CD117 suggested an adverse influence of c-kit expression on treatment outcome in AML,[19,63] but more recent studies[51-54] and our own data[60] revealed no prognostic impact of CD117 expression. In 92 adult AML patients treated according to the protocols of the German AMLCG multi-center therapy study[64] (see Figure 1) and in 103 pediatric patients of the BFM-AML90 study (data not shown), there was no significant difference between CD117 positive and CD117 negative cases as to the response to induction chemotherapy and event-free survival. In view of the heterogeneity of CD117-positive AML, which can include both poor and good prognostic subgroups [i.e. t(8;21)], this is not surprising.
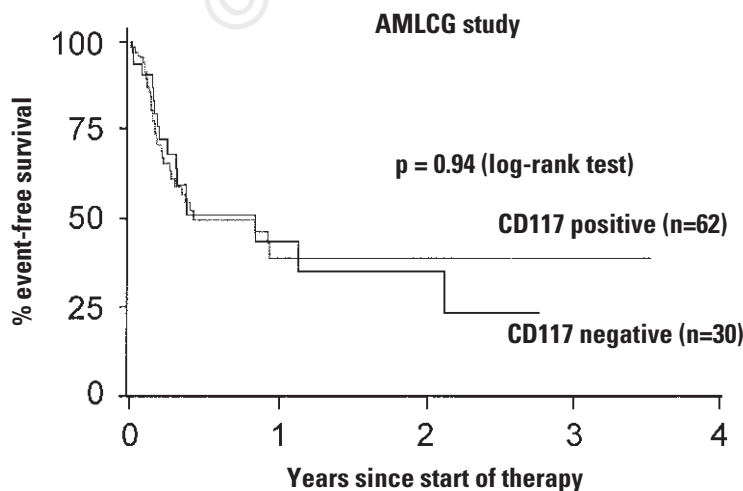

Figure 1. Event-free survival of 92 adult patients treated according to the protocol of the AMLCG 1991 trial (64), CD117 positive vs. CD117 negative.

and T-ALL, could not detect *c-kit* expression in ALL,[22,23,48,50,51,58,61] although few patients were investigated in each of these series. Based on these results, a specificity of CD117 for the myeloid lineage was postulated, which is reportedly useful for diagnostic purposes.[44,65,66] In view of some recent reports and our own data, however, the specificity of CD117 for AML has to be reconsidered. A recent report described *c-kit* expression in 4 out of 12 CD7^{+} ALL cases.[67] Only two of these, however, had cytoplasmic (cy) CD3 and could be unequivocally classified as T-lineage-derived.

In another small series 4 out of 7 T-ALL samples expressed *c-kit*.[68] Additional evidence that T-lymphoblasts might express a functional *c-kit* receptor is demonstrated by analysis of three T-cell lines derived from pediatric T-ALL. These cell lines were *c-kit* positive and in one of them SCF had a synergistic proliferative effect with IL-2.[69]

Of our group of 103 adult T-ALL, 9 (8.7%) cases were CD117-positive. All but one additionally expressed at least one myeloid antigen (CD13, CD33, CD65s).[60] All of them were TdT positive and MPO-7 negative, and most of them (n = 5) disclosed a pro-T (CD7^{+}/cyCD3^{+}/CD2^{−}/CD1a^{−}/CD3^{−}) immunophenotype. CD117 expression in B-lineage ALL is a rare event, but in a series of 753 consecutive cases of childhood B-cell-precursor ALL (pro-B-ALL, n=53; c-ALL, n=561; pre-B-ALL, n=139) we found *c-kit* expression in 22 cases (2,9%). The majority of cases were classified as c-ALL (n = 18) and the 4 remaining cases were pre-B-ALL. Interestingly, we did not observe any CD117^{+} pro-B-ALL (unpublished observations).

Conclusions

Most recent studies, including both childhood and adult AML, were unable to demonstrate any significant differences in CR rate, survival rate, and event-free survival between CD117-positive and CD117-negative cases. Therefore, these studies do not confirm previous results suggesting that CD117 contributes to the identification of clinically-relevant AML subgroups.

A small proportion of T-lineage ALL (9%), mainly consisting of immature pro-T/pre-T-ALL often with co-expression of myeloid antigens, is CD117 positive. CD117 expression is rare in B-cell-precursor-ALL and occurs in less than 3% of cases.

Despite its lack of specificity and relatively low sensitivity for the myeloid lineage, expression of CD117 in combination with other antigens might facilitate the immunologic characterization of acute leukemias,[70] especially of myeloid and early T cell origin.

References

1. Small D, Levenstein M, Kim E, et al. STK-1, the human homologue of Flk-2/Flt-3, is selectively expressed in CD34+ bone marrow cells and is involved in the proliferation of early progenitor/stem cells. Proc Natl Acad Sci USA 1994; 91:459-63.
2. Rosnet O, Birnbaum D. Hematopoietic receptors of class III receptor-type tyrosine kinases. Crit Rev Oncog 1993; 4:595-613.
3. Ullrich A, Schlessinger J. Signal transduction by receptors with tyrosine kinase activity. Cell 1990; 61:203-12.
4. Yarden Y, Kuang WJ, Yang Feng T, et al. Human proto-oncogene *c-kit*: a new cell surface receptor tyrosine kinase for an unidentified ligand. EMBO J 1987; 6:3341-51.
5. Giebel LB, Strunk KM, Holmes SA, Spritz RA. Organization and nucleotide sequence of the human KIT (mast/stem cell growth factor receptor) proto-oncogene. Oncogene 1992; 7:2207-17.
6. André C, d'Auriol L, Lacombe C, Gisselbrecht S, Galibert F. *c-kit* mRNA expression in human and murine hematopoietic cell lines. Oncogene 1989; 4:1047-9.
7. Hu ZB, Ma W, Uphoff CC, Quentmeier H, Drexler HG. *c-kit* expression in human megakaryoblastic leukemia cell lines. Blood 1994; 83:2133-44.
8. deCastro CM, Denning SM, Langdon S, et al. The *c-kit* proto-oncogene receptor is expressed on a subset of human CD3-CD4-CD8- (triple-negative) thymocytes. Exp Hematol 1994; 22:1025-33.
9. Lammie A, Drobnjak M, Gerald W, Saad A, Cote R, Cordon-Cardo C. Expression of *c-kit* and kit ligand proteins in normal human tissues. J Histochem Cytochem 1994; 42:1417-25.
10. Chui X, Egami H, Yamashita J, et al. Immunohistochemical expression of the *c-kit* proto-oncogene product in human malignant and non-malignant breast tissues. Br J Cancer 1996; 73:1233-6.
11. Hibi K, Takahashi T, Sekido Y, et al. Coexpression of the stem cell factor and the *c-kit* genes in small-cell lung cancer. Oncogene 1991; 6:2291-6.
12. Sekido Y, Takahashi T, Ueda R, et al. Recombinant human stem cell factor mediates chemotaxis of small-cell lung cancer cell lines aberrantly expressing the *c-kit* protooncogene. Cancer Res 1993; 53:1709-14.
13. Krystal GW, Hines SJ, Organ CP. Autocrine growth of small cell lung cancer mediated by coexpression of *c-kit* and stem cell factor. Cancer Res 1996; 56:370-6.
14. Hines SJ, Organ C, Kornstein MJ, Krystal GW. Coexpression of the *c-kit* and stem cell factor genes in breast carcinomas. Cell Growth Differ 1995; 6:769-79.
15. Ohashi A, Funasaka Y, Ueda M, Ichihashi M. *c-kit* receptor expression in cutaneous malignant melanoma and benign melanotic naevi. Melanoma Res 1996; 6:25-30.
16. Turner AM, Zsebo KM, Martin F, Jacobsen FW, Bennett LG, Broudy VC. Nonhematopoietic tumor cell lines express stem cell factor and display *c-kit* receptors. Blood 1992; 80:374-81.
17. Galli SJ, Zsebo KM, Geissler EN. The kit ligand, stem cell factor. Adv Immunol 1994; 55:1-96.
18. McCulloch EA, Minden MD. The cell surface receptor encoded by the proto-oncogene KIT and its ligand. Cancer Treat Res 1993; 64:45-77.
19. Gadd SJ, Ashman LK. A murine monoclonal antibody specific for a cell-surface antigen expressed by a subgroup of human myeloid leukemias. Leuk Res 1985; 9:1329-36.
20. Lerner NB, Nocka KH, Cole SR, et al. Monoclonal antibody YB5.B8 identifies the human *c-kit* protein product. Blood 1991; 77:1876-83.
21. Broudy VC, Lin N, Zsebo KM, et al. Isolation and characterization of a monoclonal antibody that recognizes the human *c-kit* receptor. Blood 1992; 79:338-46.
22. Bühring HJ, Ullrich A, Schaudt K, Müller CA, Busch FW. The product of the proto-oncogene *c-kit* (P145c-*kit*) is a human bone marrow surface antigen of hemopoietic precursor cells which is expressed on a subset of acute non-lymphoblastic leukemic cells. Leukemia 1991; 5:854-60.
23. Morita S, Tsuchiya S, Fujie H, et al. Cell surface *c-kit* receptors in human leukemia cell lines and pediatric leukemia: selective preservation of *c-kit* expression on megakaryoblastic cell lines during adaptation in vitro culture. Leukemia 1996; 10:102-5.
24. Ashman LK, Bühring HJ, Aylett GW, Broudy VC, Müller C. Epitope mapping and functional studies with three monoclonal antibodies to the *c-kit* receptor tyrosine kinase, YB5.B8, 17F11, and SR-1. J Cell Physiol 1994; 158:545-54.
25. Ashman LK, Cambareri AC, To LB, Levinsky RJ, Juttner CA. Expression of the YB5.B8 antigen (*c-kit* proto-oncogene product) in normal human bone marrow. Blood 1991; 78:30-7.
26. Strobl H, Takimoto M, Majdic O, Hocker P, Knapp W. Antigenic analysis of human haemopoietic progenitor cells expressing the growth factor receptor *c-kit*. Br J Haematol 1992; 82:287-94.
27. Simmons PJ, Aylett GW, Niutta S, To LB, Juttner CA, Ashman LK. *c-kit* is expressed by primitive human hematopoietic cells that give rise to colony-forming cells in stroma-dependent or cytokine-supplemented culture. Exp Hematol 1994; 22:157-65.
28. Gunji Y, Nakamura M, Osawa H, et al. Human primitive hematopoietic progenitor cells are more enriched in KIT^{low} cells than in KIT^{high} cells. Blood 1993; 82:3283-9.
29. McNiece IK, Langley KE, Zsebo KM. Recombinant human stem cell

factor synergises with GM-CSF, G-CSF, IL-3 and epo to stimulate human progenitor cells of the myeloid and erythroid lineages. Exp Hematol 1991; 19:226-31.

30. Broxmeyer HE, Maze R, Miyazawa K, et al. The kit receptor and its ligand, steel factor, as regulators of hemopoiesis. Cancer Cells 1991; 3:480-7.

31. Kinashi T, Springer TA. Steel factor and *c-kit* regulate cell-matrix adhesion. Blood 1994; 83:1033-8.

32. Rolink A, Streb M, Nishikawa S, Melchers F. The *c-kit*-encoded tyrosine kinase regulates the proliferation of early pre-B cells. Eur J Immunol 1991; 21:2609-12.

33. Palacios R, Nishikawa S. Developmentally regulated cell surface expression and function of *c-kit* receptor during lymphocyte ontogeny in the embryo and adult mice. Development 1992; 115:1133-47.

34. Rico-Vargas SA, Weiskopf B, Nishikawa S, Osmond DG. *c-kit* expression by B cell precursors in mouse bone marrow. Stimulation of B cell genesis by in vivo treatment with anti-*c-kit* antibody. J Immunol 1994; 152:2845-52.

35. Rolink A, Melchers F. Generation and regeneration of cells of the B-lymphocyte lineage. Curr Opin Immunol 1993; 5:207-17.

36. Takeda S, Shimizu T, Rodewald HR. Interactions between *c-kit* and stem cell factor are not required for B-cell development in vivo. Blood 1997; 89:518-25.

37. McNiece IK, Langley KE, Zsebo KM. The role of recombinant stem cell factor in early B cell development. Synergistic interaction with IL-7. J Immunol 1991; 146:3785-90.

38. Billips LG, Petitte D, Dorshkind K, Narayanan R, Chiu CP, Landreth KS. Differential roles of stromal cells, interleukin-7, and kit-ligand in the regulation of B lymphopoiesis. Blood 1992; 79:1185-92.

39. Funk PE, Varas A, Witte PL. Activity of stem cell factor and IL-7 in combination on normal bone marrow B lineage cells. J Immunol 1993; 150:748-52.

40. Wolf SS, Cohen A. Expression of cytokines and their receptors by human thymocytes and thymic stromal cells. Immunology 1992; 77:362-8.

41. Morrissey PJ, McKenna H, Widmer MB, et al. Steel factor (*c-kit* ligand) stimulates the in vitro growth of immature CD3-/CD4-/CD8-thymocytes: synergy with IL-7. Cell Immunol 1994; 157:118-31.

42. Siitonen T, Savolainen ER, Koistinen P. Expression of the *c-kit* proto-oncogene in myeloproliferative disorders and myelodysplastic syndromes. Leukemia 1994; 8:631-7.

43. Muroi K, Nakamura M, Amemiya Y, Suda T, Miura Y. Expression of *c-kit* receptor (CD117) and CD34 in leukemic cells. Leuk Lymphoma 1995; 16:297-305.

44. Valverde LR, Matutes E, Farahat N, et al. C-*kit* receptor (CD117) expression in acute leukemia. Ann Hematol 1996; 72:11-5.

45. Pinto A, Gloghini A, Gattei V, Aldinucci D, Zagonel V, Carbone A. Expression of the *c-kit* receptor in human lymphomas is restricted to Hodgkin's disease and CD30+ anaplastic large cell lymphomas. Blood 1994; 83:785-92.

46. Tomeczkowski J, Beilken A, Frick D, et al. Absence of *c-kit* receptor and absent proliferative response to stem cell factor in childhood Burkitt's lymphoma cells. Blood 1995; 86:1469-80.

47. Ocqueteau M, Orfão A, Garcia-Sanz R, Almeida J, Gonzalez M, San Miguel JF. Expression of the CD117 antigen (*c-kit*) on normal and myelomatous plasma cells. Br J Haematol 1996; 95:489-93.

48. Ikeda H, Kanakura Y, Tamaki T, et al. Expression and functional role of the proto-oncogene *c-kit* in acute myeloblastic leukemia cells. Blood 1991; 78:2962-8.

49. Broudy VC, Smith FO, Lin N, Zsebo KM, Egrie J, Bernstein ID. Blasts from patients with acute myelogenous leukemia express functional receptors for stem cell factor. Blood 1992; 80:60-7.

50. Kubota A, Okamura S, Shimoda K, Harada M, Niho Y. The *c-kit* molecule and the surface immunophenotype of human acute leukemia. Leuk Lymphoma 1994; 14:421-8.

51. Reuss-Borst MA, Bühring HJ, Schmidt H, Müller CA. AML: immunophenotypic heterogeneity and prognostic significance of c-

kit expression. Leukemia 1994; 8:258-63.

52. Smith FO, Broudy VC, Zsebo KM, et al. Cell surface expression of *c-kit* receptors by childhood acute myeloid leukemia blasts is not of prognostic value: a report from the Childrens Cancer Group. Blood 1994; 84:847-52.

53. Bradstock K, Matthews J, Benson E, Page F, Bishop J. Prognostic value of immunophenotyping in acute myeloid leukemia. Australian Leukaemia Study Group. Blood 1994; 84:1220-5.

54. Lauria F, Bagnara GP, Rondelli D, et al. Cytofluorimetric and functional analysis of *c-kit* receptor in acute leukemia. Leuk Lymphoma 1995; 18:451-5.

55. Wells SJ, Bray RA, Stempora LL, Farhi DC. CD117/CD34 expression in leukemic blasts. Am J Clin Pathol 1996; 106:192-5.

56. Hirakawa K, Kimura S, Chikayama S, Misawa S, Maekawa T. Primary acute myeloid leukemia cells negative for *c-kit* receptor protein expression do not proliferate in vitro in response to colony-stimulating factors. Leukemia 1996; 10:279-87.

57. Cole SR, Aylett GW, Harvey NL, Cambareri AC, Ashman LK. Increased expression of *c-kit* or its ligand steel factor is not a common feature of adult acute myeloid leukaemia. Leukemia 1996; 10:288-96.

58. Wang C, Curtis JE, Geissler EN, McCulloch EA, Minden MD. The expression of the proto-oncogene *c-kit* in the blast cells of acute myeloblastic leukemia. Leukemia 1989; 3:699-702.

59. Venditti A, Del Poeta G, Buccisano F, et al. Minimally differentiated acute myeloid leukemia (AML-M0): comparison of 25 cases with other French-American-British subtypes. Blood 1997; 89:621-9.

60. Sperling C, Schwartz S, Maurer J, et al. CD117 expression is restricted to myeloid and early T-lineage differentiation in acute leukemia and lacks prognostic significance in AML. Blood 1995; 86(suppl 1):40a.

61. Di Noto R, Lo Pardo C, Schiavone EM, et al. Stem cell factor receptor (*c-kit*, CD117) is expressed on blast cells from most immature types of acute myeloid malignancies but is also a characteristic of a subset of acute promyelocytic leukaemia. Br J Haematol 1996; 92:562-4.

62. Creutzig U, Harbott J, Sperling C, et al. Clinical significance of surface antigen expression in children with acute myeloid leukemia: results of study AML-BFM-87. Blood 1995; 86:3097-108.

63. Ashman LK, Roberts MM, Gadd SJ, Cooper SJ, Juttner CA. Expression of a 150-kD cell surface antigen identified by monoclonal antibody YB5.B8 is associated with poor prognosis in acute non-lymphoblastic leukaemia. Leuk Res 1988; 12:923-8.

64. Büchner T, Hiddemann W, Löffler H, et al. Improved cure rate by very early intensification combined with prolonged maintenance chemotherapy for acute myeloid leukemia (AML): data from the AML Cooperative Group. Semin Hematol 1991; 28:76-9.

65. Muroi K, Amemiya Y, Miura Y. Specificity of CD117 expression in the diagnosis of acute myeloid leukemia. Leukemia 1996; 10:1048.

66. Bené MC, Bernier M, Castoldi G, et al. Proposals for the immunological classification of acute leukemias. European Group for the Immunological Characterization of Leukemias (EGIL). Leukemia 1995; 9:1783-6.

67. Nishii K, Kita K, Miwa H, et al. *c-kit* gene expression in CD7-positive acute lymphoblastic leukemia: close correlation with expression of myeloid-associated antigen CD13. Leukemia 1992; 6:662-8.

68. Knapp W, Strobl H, Majdic O. Flow cytometric analysis of cell-surface and intracellular antigens in leukemia diagnosis. Cytometry 1994; 18:187-98.

69. Kees UR, Ashman LK. Synergistic action of interleukin-2 and Steel factor (SLF) on a human T lymphoblastoid cell line. Leukemia 1995; 9:1046-50.

70. Lanza F, Moretti S, Castagnari B, Latorraca A, Ferrarai L. Castoldi GL. Flow cytometry quantitation of IL3 and c-kit receptors in acute leukemias: clinical and biological implications [abstract]. Haematologica 1996; 81(suppl. to. n.5:80).