

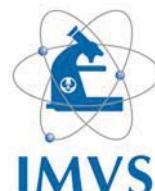
# **Molecular and Cellular Mechanisms of Increased Angiogenesis in Multiple Myeloma: A Role for CXCL12**

**Sally K. Martin**

Myeloma Research Group  
Bone and Cancer Research Laboratory,  
Division of Haematology,  
Hanson Institute  
Institute of Medical and Veterinary Science

&

Department of Medicine,  
Faculty of Health Sciences  
University of Adelaide



A thesis submitted to the University of Adelaide  
for the degree of Doctor of Philosophy  
December 2008

## **REFERENCES**

1. Grogan TM, Muller-Hermelink, H.K., Van Camp, B., Harris, N.L. and Kyle, R.A. Plasma Cell Neoplasms: Mature B-cell Neoplasms. In: Jaffe ES HN, Stein H and Vardiman JW, ed. World Health Organisation Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001:142-156.
2. Greipp PR, San Miguel J, Durie BG, *et al.* International Staging System for Multiple Myeloma. *J Clin Oncol.* 2005.
3. Katz JA, Hari P, Vesole DH. Multiple myeloma: charging toward a bright future. *CA Cancer J Clin.* 2007; 57:301-318.
4. Vacca A, Ribatti D, Roncali L, *et al.* Bone marrow angiogenesis and progression in multiple myeloma. *Br J Haematol.* 1994; 87:503-508.
5. Munshi N, Wilson, CS, Penn, J. *et al.* Angiogenesis in Newly Diagnosed Multiple Myeloma: Poor Prognosis with Increased Microvessel Density in Bone marrow Biopsies. *Blood.* 1998; 92:98.
6. Rajkumar SV, Leong T, Roche PC, *et al.* Prognostic value of bone marrow angiogenesis in multiple myeloma. *Clin Cancer Res.* 2000; 6:3111-3116.
7. Munshi NC, Wilson C. Increased bone marrow microvessel density in newly diagnosed multiple myeloma carries a poor prognosis. *Semin Oncol.* 2001; 28:565-569.
8. Pruneri G, Ponzoni M, Ferreri AJ, *et al.* Microvessel density, a surrogate marker of angiogenesis, is significantly related to survival in multiple myeloma patients. *Br J Haematol.* 2002; 118:817-820.
9. Zannettino AC, Farrugia AN, Kortesidis A, *et al.* Elevated serum levels of stromal-derived factor-1alpha are associated with increased osteoclast activity and osteolytic bone disease in multiple myeloma patients. *Cancer Res.* 2005; 65:1700-1709.
10. Salcedo R, Wasserman K, Young HA, *et al.* Vascular endothelial growth factor and basic fibroblast growth factor induce expression of CXCR4 on human endothelial cells: In vivo neovascularization induced by stromal-derived factor-1alpha. *Am J Pathol.* 1999; 154:1125-1135.
11. Salcedo R, Oppenheim JJ. Role of chemokines in angiogenesis: CXCL12/SDF-1 and CXCR4 interaction, a key regulator of endothelial cell responses. *Microcirculation.* 2003; 10:359-370.
12. Salvucci O, Yao L, Villalba S, Sajewicz A, Pittaluga S, Tosato G. Regulation of endothelial cell branching morphogenesis by endogenous chemokine stromal-derived factor-1. *Blood.* 2002; 99:2703-2711.
13. Rempel SA, Dudas S, Ge S, Gutierrez JA. Identification and localization of the cytokine SDF1 and its receptor, CXC chemokine receptor 4, to regions of necrosis and angiogenesis in human glioblastoma. *Clin Cancer Res.* 2000; 6:102-111.
14. Mirshahi F, Pourtau J, Li H, *et al.* SDF-1 activity on microvascular endothelial cells: consequences on angiogenesis in *in vitro* and *in vivo* models. *Thromb Res.* 2000; 99:587-594.
15. Ceradini DJ, Kulkarni AR, Callaghan MJ, *et al.* Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. *Nat Med.* 2004; 10:858-864.
16. MMRF. Multiple Myeloma: A Disease Overview (ed Patient Handbook). 2006.
17. San Miguel JF, Gonzalez M, Gascon A, *et al.* Immunophenotypic heterogeneity of multiple myeloma: influence on the biology and clinical course of the disease. Castellano-Leones (Spain) Cooperative Group for the Study of Monoclonal Gammopathies. *Br J Haematol.* 1991; 77:185-190.

18. Zhan F, Hardin J, Kordsmeier B, *et al.* Global gene expression profiling of multiple myeloma, monoclonal gammopathy of undetermined significance, and normal bone marrow plasma cells. *Blood*. 2002; 99:1745-1757.
19. Guikema JE, Hovenga S, Vellenga E, Bos NA. Heterogeneity in the multiple myeloma tumor clone. *Leuk Lymphoma*. 2004; 45:857-871.
20. Mateo G, Castellanos M, Rasillo A, *et al.* Genetic abnormalities and patterns of antigenic expression in multiple myeloma. *Clin Cancer Res*. 2005; 11:3661-3667.
21. Jemal A, Murray T, Ward E, *et al.* Cancer statistics, 2005. *CA Cancer J Clin*. 2005; 55:10-30.
22. Kuehl WM, Bergsagel PL. Multiple myeloma: evolving genetic events and host interactions. *Nat Rev Cancer*. 2002; 2:175-187.
23. Bergsagel PL, Chesi M, Nardini E, Brents LA, Kirby SL, Kuehl WM. Promiscuous translocations into immunoglobulin heavy chain switch regions in multiple myeloma. *Proc Natl Acad Sci U S A*. 1996; 93:13931-13936.
24. Ho PJ, Campbell LJ, Gibson J, Brown R, Joshua D. The biology and cytogenetics of multiple myeloma. *Rev Clin Exp Hematol*. 2002; 6:276-300.
25. AIHW. *Cancer In Australia: An Overview*, 2006. 2007.
26. Ries LAG, Melbert D, Krapcho M, *et al.* SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. 2007.
27. Blade J, Kyle RA. Multiple myeloma in young patients: clinical presentation and treatment approach. *Leuk Lymphoma*. 1998; 30:493-501.
28. Kyle RA, Therneau TM, Rajkumar SV, *et al.* Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2006; 354:1362-1369.
29. Kyle RA, Therneau TM, Rajkumar SV, *et al.* A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2002; 346:564-569.
30. Bergsagel D. The incidence and epidemiology of plasma cell neoplasms. *Stem Cells*. 1995; 13 Suppl 2:1-9.
31. Rajkumar SV, Kyle RA. Angiogenesis in multiple myeloma. *Semin Oncol*. 2001; 28:560-564.
32. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*. 1975; 36:842-854.
33. Tricot G, Sawyer JR, Jagannath S, *et al.* Unique role of cytogenetics in the prognosis of patients with myeloma receiving high-dose therapy and autotransplants. *J Clin Oncol*. 1997; 15:2659-2666.
34. Tricot G, Barlogie B, Jagannath S, *et al.* Poor prognosis in multiple myeloma is associated only with partial or complete deletions of chromosome 13 or abnormalities involving 11q and not with other karyotype abnormalities. *Blood*. 1995; 86:4250-4256.
35. Zhan F, Tian E, Bumm K, Smith R, Barlogie B, Shaughnessy J, Jr. Gene expression profiling of human plasma cell differentiation and classification of multiple myeloma based on similarities to distinct stages of late-stage B-cell development. *Blood*. 2003; 101:1128-1140.
36. Mundy G. Myeloma Bone Disease. *Bone Remodelling and Its Disorders*. Great Britain: Martin Dunitz Ltd; 1995:123-136.
37. Barille-Nion S, Barlogie B, Bataille R, *et al.* Advances in biology and therapy of multiple myeloma. *Hematology (Am Soc Hematol Educ Program)*. 2003:248-278.
38. Lahtinen R, Laakso M, Palva I, Virkkunen P, Elomaa I. Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. *Finnish Leukaemia Group*. *Lancet*. 1992; 340:1049-1052.

39. Callander NS, Roodman GD. Myeloma bone disease. *Semin Hematol.* 2001; 38:276-285.
40. De Raeve H, Van Marck E, Van Camp B, Vanderkerken K. Angiogenesis and the role of bone marrow endothelial cells in haematological malignancies. *Histol Histopathol.* 2004; 19:935-950.
41. Kumar S, Witzig TE, Timm M, *et al.* Bone marrow angiogenic ability and expression of angiogenic cytokines in myeloma: evidence favoring loss of marrow angiogenesis inhibitory activity with disease progression. *Blood.* 2004; 104:1159-1165.
42. Moehler TM, Hawighorst H, Neben K, *et al.* Bone marrow microcirculation analysis in multiple myeloma by contrast-enhanced dynamic magnetic resonance imaging. *Int J Cancer.* 2001; 93:862-868.
43. Coxon FP, Thompson K, Rogers MJ. Recent advances in understanding the mechanism of action of bisphosphonates. *Curr Opin Pharmacol.* 2006; 6:307-312.
44. Bergsagel DE, Sprague CC, Austin C, Griffith KM. Evaluation of new chemotherapeutic agents in the treatment of multiple myeloma. IV. L-Phenylalanine mustard (NSC-8806). *Cancer Chemother Rep.* 1962; 21:87-99.
45. Singhal S, Mehta J, Desikan R, *et al.* Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med.* 1999; 341:1565-1571.
46. Rajkumar SV, Hayman SR, Lacy MQ, *et al.* Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood.* 2005; 106:4050-4053.
47. Richardson PG, Blood E, Mitsiades CS, *et al.* A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood.* 2006; 108:3458-3464.
48. Richardson PG, Barlogie B, Berenson J, *et al.* A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med.* 2003; 348:2609-2617.
49. Richardson PG, Sonneveld P, Schuster MW, *et al.* Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med.* 2005; 352:2487-2498.
50. Dimopoulos M, Spencer A, Attal M, *et al.* Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med.* 2007; 357:2123-2132.
51. Palumbo A, Bringhen S, Caravita T, *et al.* Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet.* 2006; 367:825-831.
52. Weber DM, Chen C, Niesvizky R, *et al.* Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med.* 2007; 357:2133-2142.
53. Facon T, Mary JY, Hulin C, *et al.* Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet.* 2007; 370:1209-1218.
54. Jemal A, Siegel R, Ward E, *et al.* Cancer statistics, 2008. *CA Cancer J Clin.* 2008; 58:71-96.
55. Hideshima T, Chauhan D, Richardson P, Anderson KC. Identification and validation of novel therapeutic targets for multiple myeloma. *J Clin Oncol.* 2005; 23:6345-6350.
56. Maton A, Hopkins J, McLaughlin CW, *et al.* Human Biology and Health. Prentice Hall; 1993.
57. Adams RH, Alitalo K. Molecular regulation of angiogenesis and lymphangiogenesis. *Nat Rev Mol Cell Biol.* 2007; 8:464-478.
58. Fishman AP. Endothelium: a distributed organ of diverse capabilities. *Ann N Y Acad Sci.* 1982; 401:1-8.

59. Folkman J, Hahnfeldt P, Hlatky L. Cancer: looking outside the genome. *Nat Rev Mol Cell Biol.* 2000; 1:76-79.
60. Risau W, Flamme I. Vasculogenesis. *Annu Rev Cell Dev Biol.* 1995; 11:73-91.
61. Risau W. Mechanisms of angiogenesis. *Nature.* 1997; 386:671-674.
62. Asahara T, Murohara T, Sullivan A, *et al.* Isolation of putative progenitor endothelial cells for angiogenesis. *Science.* 1997; 275:964-967.
63. Ferrara N. Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: therapeutic implications. *Semin Oncol.* 2002; 29:10-14.
64. Ausprunk DH, Folkman J. Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during tumor angiogenesis. *Microvasc Res.* 1977; 14:53-65.
65. Djonov V, Baum O, Burri PH. Vascular remodeling by intussusceptive angiogenesis. *Cell Tissue Res.* 2003; 314:107-117.
66. Burri PH, Hlushchuk R, Djonov V. Intussusceptive angiogenesis: its emergence, its characteristics, and its significance. *Dev Dyn.* 2004; 231:474-488.
67. Djonov V, Makanya AN. New insights into intussusceptive angiogenesis. *EXS.* 2005;17-33.
68. Patan S, Munn LL, Jain RK. Intussusceptive microvascular growth in a human colon adenocarcinoma xenograft: a novel mechanism of tumor angiogenesis. *Microvasc Res.* 1996; 51:260-272.
69. Folkman J, Shing Y. Angiogenesis. *J Biol Chem.* 1992; 267:10931-10934.
70. Folkman J. Angiogenesis: an organizing principle for drug discovery? *Nat Rev Drug Discov.* 2007; 6:273-286.
71. Loughna S, Sato TN. Angiopoietin and Tie signaling pathways in vascular development. *Matrix Biol.* 2001; 20:319-325.
72. Paweletz N, Knierim M. Tumor-related angiogenesis. *Crit Rev Oncol Hematol.* 1989; 9:197-242.
73. Burger PC, Chandler DB, Klintworth GK. Corneal neovascularization as studied by scanning electron microscopy of vascular casts. *Lab Invest.* 1983; 48:169-180.
74. Burri PH, Tarek MR. A novel mechanism of capillary growth in the rat pulmonary microcirculation. *Anat Rec.* 1990; 228:35-45.
75. Burri PH, Djonov V. Intussusceptive angiogenesis--the alternative to capillary sprouting. *Mol Aspects Med.* 2002; 23:S1-27.
76. Kurz H, Burri PH, Djonov VG. Angiogenesis and vascular remodeling by intussusception: from form to function. *News Physiol Sci.* 2003; 18:65-70.
77. Djonov V, Andres AC, Ziemiecki A. Vascular remodelling during the normal and malignant life cycle of the mammary gland. *Microsc Res Tech.* 2001; 52:182-189.
78. Engerman RL, Pfaffenbach D, Davis MD. Cell turnover of capillaries. *Lab Invest.* 1967; 17:738-743.
79. Hobson B, Denekamp J. Endothelial proliferation in tumours and normal tissues: continuous labelling studies. *Br J Cancer.* 1984; 49:405-413.
80. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell.* 1996; 86:353-364.
81. Jekunen A, Kairemo K. Inhibition of angiogenesis at endothelial cell level. *Microsc Res Tech.* 2003; 60:85-97.
82. Moehler TM, Ho AD, Goldschmidt H, Barlogie B. Angiogenesis in hematologic malignancies. *Crit Rev Oncol Hematol.* 2003; 45:227-244.
83. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature.* 2003; 423:337-342.

84. Giuliani N, Colla S, Lazzaretti M, *et al*. Proangiogenic properties of human myeloma cells: production of angiopoietin-1 and its potential relationship to myeloma-induced angiogenesis. *Blood*. 2003; 102:638-645.
85. Folkman J. How is blood vessel growth regulated in normal and neoplastic tissue? G.H.A. Clowes memorial Award lecture. *Cancer Res*. 1986; 46:467-473.
86. Brem S. Angiogenesis and Cancer Control: From Concept to Therapeutic Trial. *Cancer Control*. 1999; 6:436-458.
87. Klein S, Roghani M, Rifkin DB. Fibroblast growth factors as angiogenesis factors: New insights into their mechanism of action. In: Goldberg ID, Rosen EM, eds. *Regulation of Angiogenesis*. 1997.
88. Hashizume H, Baluk P, Morikawa S, *et al*. Openings between defective endothelial cells explain tumor vessel leakiness. *Am J Pathol*. 2000; 156:1363-1380.
89. Papetti M, Herman IM. Mechanisms of normal and tumor-derived angiogenesis. *Am J Physiol Cell Physiol*. 2002; 282:C947-970.
90. Algire GH, W. CH. Vascular reactions of normal and malignant tissue in vivo. *Journal of the National Cancer Institute*. 1945; 6:73-85.
91. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971; 285:1182-1186.
92. Folkman J. Role of angiogenesis in tumor growth and metastasis. *Semin Oncol*. 2002; 29:15-18.
93. Plank MJ, Sleeman BD, Jones PF. A mathematical model of tumour angiogenesis, regulated by vascular endothelial growth factor and the angiopoietins. *J Theor Biol*. 2004; 229:435-454.
94. Brem SS, Jensen HM, Gullino PM. Angiogenesis as a marker of preneoplastic lesions of the human breast. *Cancer*. 1978; 41:239-244.
95. Jensen HM, Chen I, DeVault MR, Lewis AE. Angiogenesis induced by "normal" human breast tissue: a probable marker for precancer. *Science*. 1982; 218:293-295.
96. Lichtenbeld HC, Barendsz-Janson AF, van Essen H, Struijker Boudier H, Griffioen AW, Hillen HF. Angiogenic potential of malignant and non-malignant human breast tissues in an in vivo angiogenesis model. *Int J Cancer*. 1998; 77:455-459.
97. Uzzan B, Nicolas P, Cucherat M, Perret GY. Microvessel density as a prognostic factor in women with breast cancer: a systematic review of the literature and meta-analysis. *Cancer Res*. 2004; 64:2941-2955.
98. Galindo-Gallego M, Fernandez-Acenero MJ, Sanz-Ortega J, Aljama A, Lopez-Elzaurdia C. Prognostic significance of microvascular counts in rectal carcinoma. *Pathol Res Pract*. 2000; 196:607-612.
99. Weidner N, Carroll PR, Flax J, Blumenfeld W, Folkman J. Tumor angiogenesis correlates with metastasis in invasive prostate carcinoma. *Am J Pathol*. 1993; 143:401-409.
100. Graham CH, Rivers J, Kerbel RS, Stankiewicz KS, White WL. Extent of vascularization as a prognostic indicator in thin (< 0.76 mm) malignant melanomas. *Am J Pathol*. 1994; 145:510-514.
101. El-Assal ON, Yamanoi A, Soda Y, *et al*. Clinical significance of microvessel density and vascular endothelial growth factor expression in hepatocellular carcinoma and surrounding liver: possible involvement of vascular endothelial growth factor in the angiogenesis of cirrhotic liver. *Hepatology*. 1998; 27:1554-1562.
102. Ma J, Zhou X, Zhang T, Sun G, Meng K. [Clinicopathologic study of angiogenesis in human hepatocellular carcinoma]. *Zhonghua Bing Li Xue Za Zhi*. 2000; 29:248-251.
103. Ng IO, Poon RT, Lee JM, Fan ST, Ng M, Tso WK. Microvessel density, vascular endothelial growth factor and its receptors Flt-1 and Flk-1/KDR in hepatocellular carcinoma. *Am J Clin Pathol*. 2001; 116:838-845.

104. Park YN, Kim YB, Yang KM, Park C. Increased expression of vascular endothelial growth factor and angiogenesis in the early stage of multistep hepatocarcinogenesis. *Arch Pathol Lab Med.* 2000; 124:1061-1065.
105. Aguayo A, Kantarjian H, Mansouri T, *et al.* Angiogenesis in acute and chronic leukemias and myelodysplastic syndromes. *Blood.* 2000; 96:2240-2245.
106. Perez-Atayde AR, Sallan SE, Tedrow U, Connors S, Allred E, Folkman J. Spectrum of tumor angiogenesis in the bone marrow of children with acute lymphoblastic leukemia. *Am J Pathol.* 1997; 150:815-821.
107. Pule MA, Gullmann C, Dennis D, McMahon C, Jeffers M, Smith OP. Increased angiogenesis in bone marrow of children with acute lymphoblastic leukaemia has no prognostic significance. *Br J Haematol.* 2002; 118:991-998.
108. Hussong JW, Rodgers GM, Shami PJ. Evidence of increased angiogenesis in patients with acute myeloid leukemia. *Blood.* 2000; 95:309-313.
109. Padro T, Ruiz S, Bieker R, *et al.* Increased angiogenesis in the bone marrow of patients with acute myeloid leukemia. *Blood.* 2000; 95:2637-2644.
110. Lundberg LG, Lerner R, Sundelin P, Rogers R, Folkman J, Palmblad J. Bone marrow in polycythemia vera, chronic myelocytic leukemia, and myelofibrosis has an increased vascularity. *Am J Pathol.* 2000; 157:15-19.
111. Kini AR, Kay NE, Peterson LC. Increased bone marrow angiogenesis in B cell chronic lymphocytic leukemia. *Leukemia.* 2000; 14:1414-1418.
112. Pruneri G, Bertolini F, Soligo D, *et al.* Angiogenesis in myelodysplastic syndromes. *Br J Cancer.* 1999; 81:1398-1401.
113. Foss HD, Araujo I, Demel G, Klotzbach H, Hummel M, Stein H. Expression of vascular endothelial growth factor in lymphomas and Castleman's disease. *J Pathol.* 1997; 183:44-50.
114. Vacca A, Ribatti D, Ruco L, *et al.* Angiogenesis extent and macrophage density increase simultaneously with pathological progression in B-cell non-Hodgkin's lymphomas. *Br J Cancer.* 1999; 79:965-970.
115. Sezer O, Niemoller K, Jakob C, *et al.* Relationship between bone marrow angiogenesis and plasma cell infiltration and serum beta2-microglobulin levels in patients with multiple myeloma. *Ann Hematol.* 2001; 80:598-601.
116. Niemoller K, Jakob C, Heider U, *et al.* Bone marrow angiogenesis and its correlation with other disease characteristics in multiple myeloma in stage I versus stage II-III. *J Cancer Res Clin Oncol.* 2003; 129:234-238.
117. Kumar S, Witzig TE, Greipp PR, Rajkumar SV. Bone marrow angiogenesis and circulating plasma cells in multiple myeloma. *Br J Haematol.* 2003; 122:272-274.
118. Dankbar B, Padro T, Leo R, *et al.* Vascular endothelial growth factor and interleukin-6 in paracrine tumor-stromal cell interactions in multiple myeloma. *Blood.* 2000; 95:2630-2636.
119. Vacca A, Ribatti D. Bone marrow angiogenesis in multiple myeloma. *Leukemia.* 2006; 20:193-199.
120. Bellamy WT, Richter L, Frutiger Y, Grogan TM. Expression of vascular endothelial growth factor and its receptors in hematopoietic malignancies. *Cancer Res.* 1999; 59:728-733.
121. Kumar S, Witzig TE, Timm M, *et al.* Expression of VEGF and its receptors by myeloma cells. *Leukemia.* 2003; 17:2025-2031.
122. Sato N, Hattori Y, Wenlin D, *et al.* Elevated level of plasma basic fibroblast growth factor in multiple myeloma correlates with increased disease activity. *Jpn J Cancer Res.* 2002; 93:459-466.

123. Otsuki T, Yamada O, Yata K, *et al.* Expression of fibroblast growth factor and FGF-receptor family genes in human myeloma cells, including lines possessing t(4; 14)(q16.3; q32. 3) and FGFR3 translocation. *Int J Oncol.* 1999; 15:1205-1212.
124. Van Riet I, Hellebraut, L., Castronovo, V. *et al.* Expression of the angiogenesis-inducing molecules VEGF and bFGF in multiple myeloma and its regulation by paracrine interactions between tumour cells and stromal bone marrow cells. *Blood.* 2000; 96:Abstract 1559.
125. Di Raimondo F, Azzaro MP, Palumbo G, *et al.* Angiogenic factors in multiple myeloma: higher levels in bone marrow than in peripheral blood. *Haematologica.* 2000; 85:800-805.
126. Borset M, Hjorth-Hansen H, Seidel C, Sundan A, Waage A. Hepatocyte growth factor and its receptor c-met in multiple myeloma. *Blood.* 1996; 88:3998-4004.
127. Sezer O, Jakob C, Eucker J, *et al.* Serum levels of the angiogenic cytokines basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) in multiple myeloma. *Eur J Haematol.* 2001; 66:83-88.
128. Dominici M, Campioni D, Lanza F, *et al.* Angiogenesis in multiple myeloma: correlation between in vitro endothelial colonies growth (CFU-En) and clinical-biological features. *Leukemia.* 2001; 15:171-176.
129. Bischoff J. Approaches to studying cell adhesion molecules in angiogenesis. *Trends Cell Biol.* 1995; 5:69-74.
130. Brooks PC, Montgomery AM, Rosenfeld M, *et al.* Integrin alpha v beta 3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels. *Cell.* 1994; 79:1157-1164.
131. Eleutherakis-Papaiakovou V, Karali M, Kokkonouzis I, Tiliakos I, Dimopoulos MA. Bone marrow angiogenesis and progression in multiple myeloma: clinical significance and therapeutic approach. *Leuk Lymphoma.* 2003; 44:937-948.
132. Kerbel R, Folkman J. Clinical translation of angiogenesis inhibitors. *Nat Rev Cancer.* 2002; 2:727-739.
133. Vacca A, Ria R, Semeraro F, *et al.* Endothelial cells in the bone marrow of patients with multiple myeloma. *Blood.* 2003; 102:3340-3348.
134. Vacca A, Ribatti D, Presta M, *et al.* Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma. *Blood.* 1999; 93:3064-3073.
135. Hannan NJ, Salamonsen LA. Role of chemokines in the endometrium and in embryo implantation. *Curr Opin Obstet Gynecol.* 2007; 19:266-272.
136. Salamonsen LA, Hannan NJ, Dimitriadis E. Cytokines and chemokines during human embryo implantation: roles in implantation and early placentation. *Semin Reprod Med.* 2007; 25:437-444.
137. Broxmeyer HE, Kim CH. Regulation of hematopoiesis in a sea of chemokine family members with a plethora of redundant activities. *Exp Hematol.* 1999; 27:1113-1123.
138. Maekawa T, Ishii T. Chemokine/receptor dynamics in the regulation of hematopoiesis. *Intern Med.* 2000; 39:90-100.
139. Ono SJ, Nakamura T, Miyazaki D, Ohbayashi M, Dawson M, Toda M. Chemokines: roles in leukocyte development, trafficking, and effector function. *J Allergy Clin Immunol.* 2003; 111:1185-1199.
140. Ansel KM, Cyster JG. Chemokines in lymphopoiesis and lymphoid organ development. *Curr Opin Immunol.* 2001; 13:172-179.
141. Baggiolini M. Chemokines and leukocyte traffic. *Nature.* 1998; 392:565-568.
142. Kunkel EJ, Campbell DJ, Butcher EC. Chemokines in lymphocyte trafficking and intestinal immunity. *Microcirculation.* 2003; 10:313-323.

143. Yoshie O. Role of chemokines in trafficking of lymphocytes and dendritic cells. *Int J Hematol.* 2000; 72:399-407.
144. Gillitzer R, Goebeler M. Chemokines in cutaneous wound healing. *J Leukoc Biol.* 2001; 69:513-521.
145. Proost P, Wuyts A, van Damme J. The role of chemokines in inflammation. *Int J Clin Lab Res.* 1996; 26:211-223.
146. Taub DD, Oppenheim JJ. Chemokines, inflammation and the immune system. *Ther Immunol.* 1994; 1:229-246.
147. Mehrad B, Keane MP, Strieter RM. Chemokines as mediators of angiogenesis. *Thromb Haemost.* 2007; 97:755-762.
148. Murdoch C, Finn A. Chemokine receptors and their role in vascular biology. *J Vasc Res.* 2000; 37:1-7.
149. Locati M, Murphy PM. Chemokines and chemokine receptors: biology and clinical relevance in inflammation and AIDS. *Annu Rev Med.* 1999; 50:425-440.
150. Sallusto F, Lanzavecchia A, Mackay CR. Chemokines and chemokine receptors in T-cell priming and Th1/Th2-mediated responses. *Immunol Today.* 1998; 19:568-574.
151. Kakinuma T, Hwang ST. Chemokines, chemokine receptors, and cancer metastasis. *J Leukoc Biol.* 2006; 79:639-651.
152. O'Hayre M, Salanga CL, Handel TM, Allen SJ. Chemokines and cancer: migration, intracellular signalling and intercellular communication in the microenvironment. *Biochem J.* 2008; 409:635-649.
153. Wang JM, Deng X, Gong W, Su S. Chemokines and their role in tumor growth and metastasis. *J Immunol Methods.* 1998; 220:1-17.
154. Rollins BJ. Chemokines. *Blood.* 1997; 90:909-928.
155. Godessart N. Chemokine receptors: attractive targets for drug discovery. *Ann N Y Acad Sci.* 2005; 1051:647-657.
156. Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. *Immunity.* 2000; 12:121-127.
157. Sallusto F, Mackay CR, Lanzavecchia A. The role of chemokine receptors in primary, effector, and memory immune responses. *Annu Rev Immunol.* 2000; 18:593-620.
158. Moser B, Wolf M, Walz A, Loetscher P. Chemokines: multiple levels of leukocyte migration control. *Trends Immunol.* 2004; 25:75-84.
159. Comerford I, Nibbs RJ. Post-translational control of chemokines: a role for decoy receptors? *Immunol Lett.* 2005; 96:163-174.
160. Gough PJ, Garton KJ, Wille PT, Rychlewski M, Dempsey PJ, Raines EW. A disintegrin and metalloproteinase 10-mediated cleavage and shedding regulates the cell surface expression of CXC chemokine ligand 16. *J Immunol.* 2004; 172:3678-3685.
161. Hundhausen C, Misztela D, Berkout TA, *et al.* The disintegrin-like metalloproteinase ADAM10 is involved in constitutive cleavage of CX3CL1 (fractalkine) and regulates CX3CL1-mediated cell-cell adhesion. *Blood.* 2003; 102:1186-1195.
162. Rot A, von Andrian UH. Chemokines in innate and adaptive host defense: basic chemokine grammar for immune cells. *Annu Rev Immunol.* 2004; 22:891-928.
163. Burger JA, Kipps TJ. CXCR4: a key receptor in the crosstalk between tumor cells and their microenvironment. *Blood.* 2006; 107:1761-1767.
164. Sanz-Rodriguez F, Hidalgo A, Teixido J. Chemokine stromal cell-derived factor-1alpha modulates VLA-4 integrin-mediated multiple myeloma cell adhesion to CS-1/fibronectin and VCAM-1. *Blood.* 2001; 97:346-351.

165. Hargreaves DC, Hyman PL, Lu TT, *et al.* A coordinated change in chemokine responsiveness guides plasma cell movements. *J Exp Med.* 2001; 194:45-56.
166. Moller C, Stromberg T, Juremalm M, Nilsson K, Nilsson G. Expression and function of chemokine receptors in human multiple myeloma. *Leukemia.* 2003; 17:203-210.
167. Durig J, Schmucker U, Duhrsen U. Differential expression of chemokine receptors in B cell malignancies. *Leukemia.* 2001; 15:752-756.
168. Nakayama T, Hieshima K, Izawa D, Tatsumi Y, Kanamaru A, Yoshie O. Cutting edge: profile of chemokine receptor expression on human plasma cells accounts for their efficient recruitment to target tissues. *J Immunol.* 2003; 170:1136-1140.
169. Vande Broek I, Asosingh K, Vanderkerken K, Straetmans N, Van Camp B, Van Riet I. Chemokine receptor CCR2 is expressed by human multiple myeloma cells and mediates migration to bone marrow stromal cell-produced monocyte chemotactic proteins MCP-1, -2 and -3. *Br J Cancer.* 2003; 88:855-862.
170. Murphy PM, Baggolini M, Charo IF, *et al.* International union of pharmacology. XXII. Nomenclature for chemokine receptors. *Pharmacol Rev.* 2000; 52:145-176.
171. Yu L, Cecil J, Peng SB, *et al.* Identification and expression of novel isoforms of human stromal cell-derived factor 1. *Gene.* 2006; 374:174-179.
172. Loetscher M, Geiser T, O'Reilly T, Zwahlen R, Baggolini M, Moser B. Cloning of a human seven-transmembrane domain receptor, LESTR, that is highly expressed in leukocytes. *J Biol Chem.* 1994; 269:232-237.
173. Nagasawa T, Hirota S, Tachibana K, *et al.* Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. *Nature.* 1996; 382:635-638.
174. Delgado E, Finkel V, Baggolini M, Mackay CR, Steinman RM, Granelli-Piperno A. Mature dendritic cells respond to SDF-1, but not to several beta-chemokines. *Immunobiology.* 1998; 198:490-500.
175. Rubbert A, Combadiere C, Ostrowski M, *et al.* Dendritic cells express multiple chemokine receptors used as coreceptors for HIV entry. *J Immunol.* 1998; 160:3933-3941.
176. Sozzani S, Luini W, Borsatti A, *et al.* Receptor expression and responsiveness of human dendritic cells to a defined set of CC and CXC chemokines. *J Immunol.* 1997; 159:1993-2000.
177. Gupta SK, Lysko PG, Pillarisetti K, Ohlstein E, Stadel JM. Chemokine receptors in human endothelial cells. Functional expression of CXCR4 and its transcriptional regulation by inflammatory cytokines. *J Biol Chem.* 1998; 273:4282-4287.
178. Feil C, Augustin HG. Endothelial cells differentially express functional CXC-chemokine receptor-4 (CXCR-4/fusin) under the control of autocrine activity and exogenous cytokines. *Biochem Biophys Res Commun.* 1998; 247:38-45.
179. Hesselgesser J, Halks-Miller M, DelVecchio V, *et al.* CD4-independent association between HIV-1 gp120 and CXCR4: functional chemokine receptors are expressed in human neurons. *Curr Biol.* 1997; 7:112-121.
180. Bajetto A, Bonavia R, Barbero S, *et al.* Glial and neuronal cells express functional chemokine receptor CXCR4 and its natural ligand stromal cell-derived factor 1. *J Neurochem.* 1999; 73:2348-2357.
181. Ohtani Y, Minami M, Kawaguchi N, *et al.* Expression of stromal cell-derived factor-1 and CXCR4 chemokine receptor mRNAs in cultured rat glial and neuronal cells. *Neurosci Lett.* 1998; 249:163-166.
182. Grassi F, Cristina S, Toneguzzi S, Piacentini A, Facchini A, Lisignoli G. CXCL12 chemokine up-regulates bone resorption and MMP-9 release by human osteoclasts: CXCL12 levels are increased in synovial and bone tissue of rheumatoid arthritis patients. *J Cell Physiol.* 2004; 199:244-251.

183. Liao TS, Yurgelun MB, Chang SS, *et al.* Recruitment of osteoclast precursors by stromal cell derived factor-1 (SDF-1) in giant cell tumor of bone. *J Orthop Res.* 2005; 23:203-209.
184. Crane IJ, Wallace CA, McKillop-Smith S, Forrester JV. CXCR4 receptor expression on human retinal pigment epithelial cells from the blood-retina barrier leads to chemokine secretion and migration in response to stromal cell-derived factor 1 alpha. *J Immunol.* 2000; 165:4372-4378.
185. Murdoch C, Monk PN, Finn A. Functional expression of chemokine receptor CXCR4 on human epithelial cells. *Immunology.* 1999; 98:36-41.
186. Smith JM, Johanesen PA, Wendt MK, Binion DG, Dwinell MB. CXCL12 activation of CXCR4 regulates mucosal host defense through stimulation of epithelial cell migration and promotion of intestinal barrier integrity. *Am J Physiol Gastrointest Liver Physiol.* 2005; 288:G316-326.
187. Kowalska MA, Ratajczak J, Hoxie J, *et al.* Megakaryocyte precursors, megakaryocytes and platelets express the HIV co-receptor CXCR4 on their surface: determination of response to stromal-derived factor-1 by megakaryocytes and platelets. *Br J Haematol.* 1999; 104:220-229.
188. Riviere C, Subra F, Cohen-Solal K, *et al.* Phenotypic and functional evidence for the expression of CXCR4 receptor during megakaryocytopoiesis. *Blood.* 1999; 93:1511-1523.
189. Wang JF, Liu ZY, Groopman JE. The alpha-chemokine receptor CXCR4 is expressed on the megakaryocytic lineage from progenitor to platelets and modulates migration and adhesion. *Blood.* 1998; 92:756-764.
190. Peled A, Petit I, Kollet O, *et al.* Dependence of human stem cell engraftment and repopulation of NOD/SCID mice on CXCR4. *Science.* 1999; 283:845-848.
191. Sugiyama T, Kohara H, Noda M, Nagasawa T. Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. *Immunity.* 2006; 25:977-988.
192. Ma Q, Jones D, Springer TA. The chemokine receptor CXCR4 is required for the retention of B lineage and granulocytic precursors within the bone marrow microenvironment. *Immunity.* 1999; 10:463-471.
193. Nagasawa T, Kikutani H, Kishimoto T. Molecular cloning and structure of a pre-B-cell growth-stimulating factor. *Proc Natl Acad Sci U S A.* 1994; 91:2305-2309.
194. Bleul CC, Schultze JL, Springer TA. B lymphocyte chemotaxis regulated in association with microanatomic localization, differentiation state, and B cell receptor engagement. *J Exp Med.* 1998; 187:753-762.
195. Hernandez-Lopez C, Varas A, Sacedon R, *et al.* Stromal cell-derived factor 1/CXCR4 signaling is critical for early human T-cell development. *Blood.* 2002; 99:546-554.
196. Broxmeyer HE, Kohli L, Kim CH, *et al.* Stromal cell-derived factor-1/CXCL12 directly enhances survival/antiapoptosis of myeloid progenitor cells through CXCR4 and G(alpha)i proteins and enhances engraftment of competitive, repopulating stem cells. *J Leukoc Biol.* 2003; 73:630-638.
197. Chalasani SH, Sabelko KA, Sunshine MJ, Littman DR, Raper JA. A chemokine, SDF-1, reduces the effectiveness of multiple axonal repellents and is required for normal axon pathfinding. *J Neurosci.* 2003; 23:1360-1371.
198. Jaleel MA, Tsai AC, Sarkar S, Freedman PV, Rubin LP. Stromal cell-derived factor-1 (SDF-1) signalling regulates human placental trophoblast cell survival. *Mol Hum Reprod.* 2004; 10:901-909.

199. Kortesidis A, Zannettino A, Isenmann S, Shi S, Lapidot T, Gronthos S. Stromal-derived factor-1 promotes the growth, survival, and development of human bone marrow stromal stem cells. *Blood*. 2005; 105:3793-3801.
200. Wright LM, Maloney W, Yu X, Kindle L, Collin-Osdoby P, Osdoby P. Stromal cell-derived factor-1 binding to its chemokine receptor CXCR4 on precursor cells promotes the chemotactic recruitment, development and survival of human osteoclasts. *Bone*. 2005; 36:840-853.
201. Bleul CC, Fuhrbrigge RC, Casasnovas JM, Aiuti A, Springer TA. A highly efficacious lymphocyte chemoattractant, stromal cell-derived factor 1 (SDF-1). *J Exp Med*. 1996; 184:1101-1109.
202. Vecchi A, Massimiliano L, Ramponi S, *et al*. Differential responsiveness to constitutive vs. inducible chemokines of immature and mature mouse dendritic cells. *J Leukoc Biol*. 1999; 66:489-494.
203. Koshiba T, Hosotani R, Miyamoto Y, *et al*. Expression of stromal cell-derived factor 1 and CXCR4 ligand receptor system in pancreatic cancer: a possible role for tumor progression. *Clin Cancer Res*. 2000; 6:3530-3535.
204. Siveke JT, Hamann A. T helper 1 and T helper 2 cells respond differentially to chemokines. *J Immunol*. 1998; 160:550-554.
205. Lazarini F, Tham TN, Casanova P, Arenzana-Seisdedos F, Dubois-Dalcq M. Role of the alpha-chemokine stromal cell-derived factor (SDF-1) in the developing and mature central nervous system. *Glia*. 2003; 42:139-148.
206. Yu X, Huang Y, Collin-Osdoby P, Osdoby P. Stromal cell-derived factor-1 (SDF-1) recruits osteoclast precursors by inducing chemotaxis, matrix metalloproteinase-9 (MMP-9) activity, and collagen transmigration. *J Bone Miner Res*. 2003; 18:1404-1418.
207. Ma Q, Jones D, Borghesani PR, *et al*. Impaired B-lymphopoiesis, myelopoiesis, and derailed cerebellar neuron migration in CXCR4- and SDF-1-deficient mice. *Proc Natl Acad Sci U S A*. 1998; 95:9448-9453.
208. Tachibana K, Hirota S, Iizasa H, *et al*. The chemokine receptor CXCR4 is essential for vascularization of the gastrointestinal tract. *Nature*. 1998; 393:591-594.
209. Balabanian K, Lagane B, Infantino S, *et al*. The chemokine SDF-1/CXCL12 binds to and signals through the orphan receptor RDC1 in T lymphocytes. *J Biol Chem*. 2005; 280:35760-35766.
210. Burns JM, Summers BC, Wang Y, *et al*. A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development. *J Exp Med*. 2006; 203:2201-2213.
211. Sierro F, Biben C, Martinez-Munoz L, *et al*. Disrupted cardiac development but normal hematopoiesis in mice deficient in the second CXCL12/SDF-1 receptor, CXCR7. *Proc Natl Acad Sci U S A*. 2007; 104:14759-14764.
212. Infantino S, Moepps B, Thelen M. Expression and regulation of the orphan receptor RDC1 and its putative ligand in human dendritic and B cells. *J Immunol*. 2006; 176:2197-2207.
213. De La Luz Sierra M, Yang F, Narazaki M, *et al*. Differential processing of stromal-derived factor-1alpha and stromal-derived factor-1beta explains functional diversity. *Blood*. 2004; 103:2452-2459.
214. Levesque JP, Hendy J, Takamatsu Y, Simmons PJ, Bendall LJ. Disruption of the CXCR4/CXCL12 chemotactic interaction during hematopoietic stem cell mobilization induced by GCSF or cyclophosphamide. *J Clin Invest*. 2003; 111:187-196.

215. Petit I, Szyper-Kravitz M, Nagler A, *et al.* G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. *Nat Immunol.* 2002; 3:687-694.
216. Gomperts BN, Belperio JA, Rao PN, *et al.* Circulating progenitor epithelial cells traffic via CXCR4/CXCL12 in response to airway injury. *J Immunol.* 2006; 176:1916-1927.
217. Scotton CJ, Wilson JL, Milliken D, Stamp G, Balkwill FR. Epithelial cancer cell migration: a role for chemokine receptors? *Cancer Res.* 2001; 61:4961-4965.
218. Zou W, Machelon V, Coulomb-L'Hermin A, *et al.* Stromal-derived factor-1 in human tumors recruits and alters the function of plasmacytoid precursor dendritic cells. *Nat Med.* 2001; 7:1339-1346.
219. Kang H, Watkins G, Parr C, Douglas-Jones A, Mansel RE, Jiang WG. Stromal cell derived factor-1: its influence on invasiveness and migration of breast cancer cells in vitro, and its association with prognosis and survival in human breast cancer. *Breast Cancer Res.* 2005; 7:R402-410.
220. Hwang JH, Hwang JH, Chung HK, *et al.* CXC chemokine receptor 4 expression and function in human anaplastic thyroid cancer cells. *J Clin Endocrinol Metab.* 2003; 88:408-416.
221. Sun YX, Wang J, Shelburne CE, *et al.* Expression of CXCR4 and CXCL12 (SDF-1) in human prostate cancers (PCa) in vivo. *J Cell Biochem.* 2003; 89:462-473.
222. Barbero S, Bonavia R, Bajetto A, *et al.* Stromal cell-derived factor 1alpha stimulates human glioblastoma cell growth through the activation of both extracellular signal-regulated kinases 1/2 and Akt. *Cancer Res.* 2003; 63:1969-1974.
223. Ishigami S, Natsugoe S, Okumura H, *et al.* Clinical implication of CXCL12 expression in gastric cancer. *Ann Surg Oncol.* 2007; 14:3154-3158.
224. Muller A, Homey B, Soto H, *et al.* Involvement of chemokine receptors in breast cancer metastasis. *Nature.* 2001; 410:50-56.
225. Li YM, Pan Y, Wei Y, *et al.* Upregulation of CXCR4 is essential for HER2-mediated tumor metastasis. *Cancer Cell.* 2004; 6:459-469.
226. Darash-Yahana M, Pikarsky E, Abramovitch R, *et al.* Role of high expression levels of CXCR4 in tumor growth, vascularization, and metastasis. *Faseb J.* 2004; 18:1240-1242.
227. Taichman RS, Cooper C, Keller ET, Pienta KJ, Taichman NS, McCauley LK. Use of the stromal cell-derived factor-1/CXCR4 pathway in prostate cancer metastasis to bone. *Cancer Res.* 2002; 62:1832-1837.
228. Milliken D, Scotton C, Raju S, Balkwill F, Wilson J. Analysis of chemokines and chemokine receptor expression in ovarian cancer ascites. *Clin Cancer Res.* 2002; 8:1108-1114.
229. Marchesi F, Monti P, Leone BE, *et al.* Increased survival, proliferation, and migration in metastatic human pancreatic tumor cells expressing functional CXCR4. *Cancer Res.* 2004; 64:8420-8427.
230. Ding Y, Shimada Y, Maeda M, *et al.* Association of CC chemokine receptor 7 with lymph node metastasis of esophageal squamous cell carcinoma. *Clin Cancer Res.* 2003; 9:3406-3412.
231. Kaifi JT, Yekebas EF, Schurr P, *et al.* Tumor-cell homing to lymph nodes and bone marrow and CXCR4 expression in esophageal cancer. *J Natl Cancer Inst.* 2005; 97:1840-1847.
232. Phillips RJ, Burdick MD, Lutz M, Belperio JA, Keane MP, Strieter RM. The stromal derived factor-1/CXCL12-CXC chemokine receptor 4 biological axis in non-small cell lung cancer metastases. *Am J Respir Crit Care Med.* 2003; 167:1676-1686.

233. Schrader AJ, Lechner O, Templin M, *et al.* CXCR4/CXCL12 expression and signalling in kidney cancer. *Br J Cancer*. 2002; 86:1250-1256.
234. Castellone MD, Guarino V, De Falco V, *et al.* Functional expression of the CXCR4 chemokine receptor is induced by RET/PTC oncogenes and is a common event in human papillary thyroid carcinomas. *Oncogene*. 2004; 23:5958-5967.
235. Eisenhardt A, Frey U, Tack M, *et al.* Expression analysis and potential functional role of the CXCR4 chemokine receptor in bladder cancer. *Eur Urol*. 2005; 47:111-117.
236. Laverdiere C, Hoang BH, Yang R, *et al.* Messenger RNA expression levels of CXCR4 correlate with metastatic behavior and outcome in patients with osteosarcoma. *Clin Cancer Res*. 2005; 11:2561-2567.
237. Mohle R, Failenschmid C, Bautz F, Kanz L. Overexpression of the chemokine receptor CXCR4 in B cell chronic lymphocytic leukemia is associated with increased functional response to stromal cell-derived factor-1 (SDF-1). *Leukemia*. 1999; 13:1954-1959.
238. Corcione A, Arduino N, Ferretti E, *et al.* Chemokine receptor expression and function in childhood acute lymphoblastic leukemia of B-lineage. *Leuk Res*. 2006; 30:365-372.
239. Schimanski CC, Schwald S, Simiantonaki N, *et al.* Effect of chemokine receptors CXCR4 and CCR7 on the metastatic behavior of human colorectal cancer. *Clin Cancer Res*. 2005; 11:1743-1750.
240. Schimanski CC, Bahre R, Gockel I, *et al.* Dissemination of hepatocellular carcinoma is mediated via chemokine receptor CXCR4. *Br J Cancer*. 2006; 95:210-217.
241. Bonavia R, Bajetto A, Barbero S, Pirani P, Florio T, Schettini G. Chemokines and their receptors in the CNS: expression of CXCL12/SDF-1 and CXCR4 and their role in astrocyte proliferation. *Toxicol Lett*. 2003; 139:181-189.
242. Orimo A, Gupta PB, Sgroi DC, *et al.* Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell*. 2005; 121:335-348.
243. Sehgal A, Keener C, Boynton AL, Warrick J, Murphy GP. CXCR-4, a chemokine receptor, is overexpressed in and required for proliferation of glioblastoma tumor cells. *J Surg Oncol*. 1998; 69:99-104.
244. Kijima T, Maulik G, Ma PC, *et al.* Regulation of cellular proliferation, cytoskeletal function, and signal transduction through CXCR4 and c-Kit in small cell lung cancer cells. *Cancer Res*. 2002; 62:6304-6311.
245. Burger M, Glodek A, Hartmann T, *et al.* Functional expression of CXCR4 (CD184) on small-cell lung cancer cells mediates migration, integrin activation, and adhesion to stromal cells. *Oncogene*. 2003; 22:8093-8101.
246. Hartmann TN, Burger JA, Glodek A, Fujii N, Burger M. CXCR4 chemokine receptor and integrin signaling co-operate in mediating adhesion and chemoresistance in small cell lung cancer (SCLC) cells. *Oncogene*. 2005; 24:4462-4471.
247. Kryczek I, Lange A, Mottram P, *et al.* CXCL12 and vascular endothelial growth factor synergistically induce neoangiogenesis in human ovarian cancers. *Cancer Res*. 2005; 65:465-472.
248. Strieter RM, Polverini PJ, Kunkel SL, *et al.* The functional role of the ELR motif in CXC chemokine-mediated angiogenesis. *J Biol Chem*. 1995; 270:27348-27357.
249. Volin MV, Joseph L, Shockley MS, Davies PF. Chemokine receptor CXCR4 expression in endothelium. *Biochem Biophys Res Commun*. 1998; 242:46-53.

250. Heidemann J, Ogawa H, Rafiee P, *et al*. Mucosal angiogenesis regulation by CXCR4 and its ligand CXCL12 expressed by human intestinal microvascular endothelial cells. *Am J Physiol Gastrointest Liver Physiol*. 2004; 286:G1059-1068.
251. Murdoch C, Monk PN, Finn A. Cxc chemokine receptor expression on human endothelial cells. *Cytokine*. 1999; 11:704-712.
252. Salcedo R, Resau JH, Halverson D, *et al*. Differential expression and responsiveness of chemokine receptors (CXCR1-3) by human microvascular endothelial cells and umbilical vein endothelial cells. *Faseb J*. 2000; 14:2055-2064.
253. Salcedo R, Zhang X, Young HA, *et al*. Angiogenic effects of prostaglandin E2 are mediated by up-regulation of CXCR4 on human microvascular endothelial cells. *Blood*. 2003; 102:1966-1977.
254. Salmaggi A, Gelati M, Pollo B, *et al*. CXCL12 in malignant glial tumors: a possible role in angiogenesis and cross-talk between endothelial and tumoral cells. *J Neurooncol*. 2004; 67:305-317.
255. Neuhaus T, Stier S, Totzke G, *et al*. Stromal cell-derived factor 1alpha (SDF-1alpha) induces gene-expression of early growth response-1 (Egr-1) and VEGF in human arterial endothelial cells and enhances VEGF induced cell proliferation. *Cell Prolif*. 2003; 36:75-86.
256. De Falco E, Porcelli D, Torella AR, *et al*. SDF-1 involvement in endothelial phenotype and ischemia-induced recruitment of bone marrow progenitor cells. *Blood*. 2004; 104:3472-3482.
257. Pablos JL, Santiago B, Galindo M, *et al*. Synoviocyte-derived CXCL12 is displayed on endothelium and induces angiogenesis in rheumatoid arthritis. *J Immunol*. 2003; 170:2147-2152.
258. Schneider GP, Salcedo R, Dong HF, Kleinman HK, Oppenheim JJ, Howard OM. Suradista NSC 651016 inhibits the angiogenic activity of CXCL12-stromal cell-derived factor 1alpha. *Clin Cancer Res*. 2002; 8:3955-3960.
259. Butler JM, Guthrie SM, Koc M, *et al*. SDF-1 is both necessary and sufficient to promote proliferative retinopathy. *J Clin Invest*. 2005; 115:86-93.
260. Menu E, Asosingh K, Indraccolo S, *et al*. The involvement of stromal derived factor 1alpha in homing and progression of multiple myeloma in the 5TMM model. *Haematologica*. 2006; 91:605-612.
261. Al Rayes MH, Rawstron AC, Morgan GJ, Davies FE. The bone marrow microenvironment influences the differential chemokine receptor expression of normal and neoplastic plasma cells. *Blood*. 2005; 105:4895-4896.
262. Trentin L, Miorin M, Facco M, *et al*. Multiple myeloma plasma cells show different chemokine receptor profiles at sites of disease activity. *Br J Haematol*. 2007; 138:594-602.
263. Alsayed Y, Ngo H, Runnels J, *et al*. Mechanisms of regulation of CXCR4/SDF-1 (CXCL12)-dependent migration and homing in multiple myeloma. *Blood*. 2007; 109:2708-2717.
264. Parmo-Cabanas M, Molina-Ortiz I, Matias-Roman S, *et al*. Role of metalloproteinases MMP-9 and MT1-MMP in CXCL12-promoted myeloma cell invasion across basement membranes. *J Pathol*. 2006; 208:108-118.
265. Parmo-Cabanas M, Bartolome RA, Wright N, Hidalgo A, Drager AM, Teixido J. Integrin alpha4beta1 involvement in stromal cell-derived factor-1alpha-promoted myeloma cell transendothelial migration and adhesion: role of cAMP and the actin cytoskeleton in adhesion. *Exp Cell Res*. 2004; 294:571-580.
266. Gazitt Y, Akay C. Mobilization of myeloma cells involves SDF-1/CXCR4 signaling and downregulation of VLA-4. *Stem Cells*. 2004; 22:65-73.

267. Kawabata K, Ujikawa M, Egawa T, *et al.* A cell-autonomous requirement for CXCR4 in long-term lymphoid and myeloid reconstitution. *Proc Natl Acad Sci U S A*. 1999; 96:5663-5667.
268. Hideshima T, Chauhan D, Hayashi T, *et al.* The biological sequelae of stromal cell-derived factor-1alpha in multiple myeloma. *Mol Cancer Ther*. 2002; 1:539-544.
269. Semenza GL. Hydroxylation of HIF-1: oxygen sensing at the molecular level. *Physiology (Bethesda)*. 2004; 19:176-182.
270. Hockel M, Vaupel P. Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects. *J Natl Cancer Inst*. 2001; 93:266-276.
271. Semenza GL. HIF-1 and human disease: one highly involved factor. *Genes Dev*. 2000; 14:1983-1991.
272. Manalo DJ, Rowan A, Lavoie T, *et al.* Transcriptional regulation of vascular endothelial cell responses to hypoxia by HIF-1. *Blood*. 2005; 105:659-669.
273. Jiang BH, Zheng JZ, Leung SW, Roe R, Semenza GL. Transactivation and inhibitory domains of hypoxia-inducible factor 1alpha. Modulation of transcriptional activity by oxygen tension. *J Biol Chem*. 1997; 272:19253-19260.
274. Semenza G. Signal transduction to hypoxia-inducible factor 1. *Biochem Pharmacol*. 2002; 64:993-998.
275. Semenza GL. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer*. 2003; 3:721-732.
276. Semenza GL. Angiogenesis in ischemic and neoplastic disorders. *Annu Rev Med*. 2003; 54:17-28.
277. Chi JT, Wang Z, Nuyten DS, *et al.* Gene expression programs in response to hypoxia: cell type specificity and prognostic significance in human cancers. *PLoS Med*. 2006; 3:e47.
278. Wang GL, Semenza GL. Characterization of hypoxia-inducible factor 1 and regulation of DNA binding activity by hypoxia. *J Biol Chem*. 1993; 268:21513-21518.
279. Wiesener MS, Turley H, Allen WE, *et al.* Induction of endothelial PAS domain protein-1 by hypoxia: characterization and comparison with hypoxia-inducible factor-1alpha. *Blood*. 1998; 92:2260-2268.
280. Oikawa M, Abe M, Kurosawa H, Hida W, Shirato K, Sato Y. Hypoxia induces transcription factor ETS-1 via the activity of hypoxia-inducible factor-1. *Biochem Biophys Res Commun*. 2001; 289:39-43.
281. Taylor CT, Furuta GT, Synnestvedt K, Colgan SP. Phosphorylation-dependent targeting of cAMP response element binding protein to the ubiquitin/proteasome pathway in hypoxia. *Proc Natl Acad Sci U S A*. 2000; 97:12091-12096.
282. Bandyopadhyay RS, Phelan M, Faller DV. Hypoxia induces AP-1-regulated genes and AP-1 transcription factor binding in human endothelial and other cell types. *Biochim Biophys Acta*. 1995; 1264:72-78.
283. Rupec RA, Baeuerle PA. The genomic response of tumor cells to hypoxia and reoxygenation. Differential activation of transcription factors AP-1 and NF-kappa B. *Eur J Biochem*. 1995; 234:632-640.
284. Yao KS, Xanthoudakis S, Curran T, O'Dwyer PJ. Activation of AP-1 and of a nuclear redox factor, Ref-1, in the response of HT29 colon cancer cells to hypoxia. *Mol Cell Biol*. 1994; 14:5997-6003.
285. Schmedtje JF, Jr., Ji YS, Liu WL, DuBois RN, Runge MS. Hypoxia induces cyclooxygenase-2 via the NF-kappaB p65 transcription factor in human vascular endothelial cells. *J Biol Chem*. 1997; 272:601-608.
286. Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O<sub>2</sub> tension. *Proc Natl Acad Sci U S A*. 1995; 92:5510-5514.

287. Kallio PJ, Wilson WJ, O'Brien S, Makino Y, Poellinger L. Regulation of the hypoxia-inducible transcription factor 1alpha by the ubiquitin-proteasome pathway. *J Biol Chem.* 1999; 274:6519-6525.
288. Semenza GL. Hypoxia-inducible factor 1: oxygen homeostasis and disease pathophysiology. *Trends Mol Med.* 2001; 7:345-350.
289. Jiang BH, Rue E, Wang GL, Roe R, Semenza GL. Dimerization, DNA binding, and transactivation properties of hypoxia-inducible factor 1. *J Biol Chem.* 1996; 271:17771-17778.
290. Pugh CW, O'Rourke JF, Nagao M, Gleadle JM, Ratcliffe PJ. Activation of hypoxia-inducible factor-1; definition of regulatory domains within the alpha subunit. *J Biol Chem.* 1997; 272:11205-11214.
291. Gothie E, Richard DE, Berra E, Pages G, Pouyssegur J. Identification of alternative spliced variants of human hypoxia-inducible factor-1alpha. *J Biol Chem.* 2000; 275:6922-6927.
292. Chun YS, Choi E, Kim TY, Kim MS, Park JW. A dominant-negative isoform lacking exons 11 and 12 of the human hypoxia-inducible factor-1alpha gene. *Biochem J.* 2002; 362:71-79.
293. Tian H, McKnight SL, Russell DW. Endothelial PAS domain protein 1 (EPAS1), a transcription factor selectively expressed in endothelial cells. *Genes Dev.* 1997; 11:72-82.
294. Ema M, Taya S, Yokotani N, Sogawa K, Matsuda Y, Fujii-Kuriyama Y. A novel bHLH-PAS factor with close sequence similarity to hypoxia-inducible factor 1alpha regulates the VEGF expression and is potentially involved in lung and vascular development. *Proc Natl Acad Sci U S A.* 1997; 94:4273-4278.
295. Talks KL, Turley H, Gatter KC, *et al.* The expression and distribution of the hypoxia-inducible factors HIF-1alpha and HIF-2alpha in normal human tissues, cancers, and tumor-associated macrophages. *Am J Pathol.* 2000; 157:411-421.
296. Tian H, Hammer RE, Matsumoto AM, Russell DW, McKnight SL. The hypoxia-responsive transcription factor EPAS1 is essential for catecholamine homeostasis and protection against heart failure during embryonic development. *Genes Dev.* 1998; 12:3320-3324.
297. Wiesener MS, Jurgensen JS, Rosenberger C, *et al.* Widespread hypoxia-inducible expression of HIF-2alpha in distinct cell populations of different organs. *Faseb J.* 2003; 17:271-273.
298. Chavez JC, Baranova O, Lin J, Pichiule P. The transcriptional activator hypoxia inducible factor 2 (HIF-2/EPAS-1) regulates the oxygen-dependent expression of erythropoietin in cortical astrocytes. *J Neurosci.* 2006; 26:9471-9481.
299. Camenisch G, Stroka DM, Gassmann M, Wenger RH. Attenuation of HIF-1 DNA-binding activity limits hypoxia-inducible endothelin-1 expression. *Pflugers Arch.* 2001; 443:240-249.
300. Hu CJ, Wang LY, Chodosh LA, Keith B, Simon MC. Differential roles of hypoxia-inducible factor 1alpha (HIF-1alpha) and HIF-2alpha in hypoxic gene regulation. *Mol Cell Biol.* 2003; 23:9361-9374.
301. Sowter HM, Raval RR, Moore JW, Ratcliffe PJ, Harris AL. Predominant role of hypoxia-inducible transcription factor (Hif)-1alpha versus Hif-2alpha in regulation of the transcriptional response to hypoxia. *Cancer Res.* 2003; 63:6130-6134.
302. Iyer NV, Kotch LE, Agani F, *et al.* Cellular and developmental control of O<sub>2</sub> homeostasis by hypoxia-inducible factor 1 alpha. *Genes Dev.* 1998; 12:149-162.
303. Ryan HE, Lo J, Johnson RS. HIF-1 alpha is required for solid tumor formation and embryonic vascularization. *Embo J.* 1998; 17:3005-3015.

304. Kline DD, Peng YJ, Manalo DJ, Semenza GL, Prabhakar NR. Defective carotid body function and impaired ventilatory responses to chronic hypoxia in mice partially deficient for hypoxia-inducible factor 1 alpha. *Proc Natl Acad Sci U S A*. 2002; 99:821-826.
305. Yu AY, Shimoda LA, Iyer NV, *et al*. Impaired physiological responses to chronic hypoxia in mice partially deficient for hypoxia-inducible factor 1alpha. *J Clin Invest*. 1999; 103:691-696.
306. Peng J, Zhang L, Drysdale L, Fong GH. The transcription factor EPAS-1/hypoxia-inducible factor 2alpha plays an important role in vascular remodeling. *Proc Natl Acad Sci U S A*. 2000; 97:8386-8391.
307. Compernolle V, Brusselmans K, Acker T, *et al*. Loss of HIF-2alpha and inhibition of VEGF impair fetal lung maturation, whereas treatment with VEGF prevents fatal respiratory distress in premature mice. *Nat Med*. 2002; 8:702-710.
308. Scortegagna M, Ding K, Oktay Y, *et al*. Multiple organ pathology, metabolic abnormalities and impaired homeostasis of reactive oxygen species in Epas1<sup>-/-</sup> mice. *Nat Genet*. 2003; 35:331-340.
309. Scortegagna M, Morris MA, Oktay Y, Bennett M, Garcia JA. The HIF family member EPAS1/HIF-2alpha is required for normal hematopoiesis in mice. *Blood*. 2003; 102:1634-1640.
310. Maynard MA, Qi H, Chung J, *et al*. Multiple splice variants of the human HIF-3 alpha locus are targets of the von Hippel-Lindau E3 ubiquitin ligase complex. *J Biol Chem*. 2003; 278:11032-11040.
311. Huang LE, Arany Z, Livingston DM, Bunn HF. Activation of hypoxia-inducible transcription factor depends primarily upon redox-sensitive stabilization of its alpha subunit. *J Biol Chem*. 1996; 271:32253-32259.
312. Huang LE, Gu J, Schau M, Bunn HF. Regulation of hypoxia-inducible factor 1alpha is mediated by an O<sub>2</sub>-dependent degradation domain via the ubiquitin-proteasome pathway. *Proc Natl Acad Sci U S A*. 1998; 95:7987-7992.
313. Kallio PJ, Pongratz I, Gradin K, McGuire J, Poellinger L. Activation of hypoxia-inducible factor 1alpha: posttranscriptional regulation and conformational change by recruitment of the Arnt transcription factor. *Proc Natl Acad Sci U S A*. 1997; 94:5667-5672.
314. Powell JD, Elshein R, Forest DJ, Palladino MA. Stimulation of hypoxia-inducible factor-1 alpha (HIF-1alpha) protein in the adult rat testis following ischemic injury occurs without an increase in HIF-1alpha messenger RNA expression. *Biol Reprod*. 2002; 67:995-1002.
315. Wenger RH, Kvietikova I, Rolfs A, Gassmann M, Marti HH. Hypoxia-inducible factor-1 alpha is regulated at the post-mRNA level. *Kidney Int*. 1997; 51:560-563.
316. Berra E, Benizri E, Ginouves A, Volmat V, Roux D, Pouyssegur J. HIF prolyl-hydroxylase 2 is the key oxygen sensor setting low steady-state levels of HIF-1alpha in normoxia. *Embo J*. 2003; 22:4082-4090.
317. Bruick RK, McKnight SL. A conserved family of prolyl-4-hydroxylases that modify HIF. *Science*. 2001; 294:1337-1340.
318. Epstein AC, Gleadle JM, McNeill LA, *et al*. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. *Cell*. 2001; 107:43-54.
319. Ivan M, Kondo K, Yang H, *et al*. HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O<sub>2</sub> sensing. *Science*. 2001; 292:464-468.
320. Jaakkola P, Mole DR, Tian YM, *et al*. Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O<sub>2</sub>-regulated prolyl hydroxylation. *Science*. 2001; 292:468-472.

321. Maxwell PH, Wiesener MS, Chang GW, *et al.* The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature*. 1999; 399:271-275.
322. Salceda SaC, J. Hypoxia-inducible factor 1alpha (HIF-1alpha) protein is rapidly degraded by the ubiquitin-proteasome system under normoxic conditions. Its stabilization by hypoxia depends on redox-induced changes. *J Biol Chem*. 1997; 272:22642-22647.
323. Carrero P, Okamoto K, Coumailleau P, O'Brien S, Tanaka H, Poellinger L. Redox-regulated recruitment of the transcriptional coactivators CREB-binding protein and SRC-1 to hypoxia-inducible factor 1alpha. *Mol Cell Biol*. 2000; 20:402-415.
324. Okino ST, Chichester CH, Whitlock JP, Jr. Hypoxia-inducible mammalian gene expression analyzed *in vivo* at a TATA-driven promoter and at an initiator-driven promoter. *J Biol Chem*. 1998; 273:23837-23843.
325. Richard DE, Berra E, Gothie E, Roux D, Pouyssegur J. p42/p44 mitogen-activated protein kinases phosphorylate hypoxia-inducible factor 1alpha (HIF-1alpha) and enhance the transcriptional activity of HIF-1. *J Biol Chem*. 1999; 274:32631-32637.
326. Semenza GL. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. *J Appl Physiol*. 2000; 88:1474-1480.
327. Bracken CP, Fedele AO, Linke S, *et al.* Cell-specific regulation of hypoxia-inducible factor (HIF)-1alpha and HIF-2alpha stabilization and transactivation in a graded oxygen environment. *J Biol Chem*. 2006; 281:22575-22585.
328. Holmquist-Mengelbier L, Fredlund E, Lofstedt T, *et al.* Recruitment of HIF-1alpha and HIF-2alpha to common target genes is differentially regulated in neuroblastoma: HIF-2alpha promotes an aggressive phenotype. *Cancer Cell*. 2006; 10:413-423.
329. Jewell UR, Kvietikova I, Scheid A, Bauer C, Wenger RH, Gassmann M. Induction of HIF-1alpha in response to hypoxia is instantaneous. *Faseb J*. 2001; 15:1312-1314.
330. Brahimi-Horn C, Mazure N, Pouyssegur J. Signalling via the hypoxia-inducible factor-1alpha requires multiple posttranslational modifications. *Cell Signal*. 2005; 17:1-9.
331. Lando D, Peet DJ, Gorman JJ, Whelan DA, Whitelaw ML, Bruick RK. FIH-1 is an asparaginyl hydroxylase enzyme that regulates the transcriptional activity of hypoxia-inducible factor. *Genes Dev*. 2002; 16:1466-1471.
332. Jeong JW, Bae MK, Ahn MY, *et al.* Regulation and destabilization of HIF-1alpha by ARD1-mediated acetylation. *Cell*. 2002; 111:709-720.
333. Sodhi A, Montaner S, Patel V, *et al.* The Kaposi's sarcoma-associated herpes virus G protein-coupled receptor up-regulates vascular endothelial growth factor expression and secretion through mitogen-activated protein kinase and p38 pathways acting on hypoxia-inducible factor 1alpha. *Cancer Res*. 2000; 60:4873-4880.
334. Suzuki H, Tomida A, Tsuruo T. Dephosphorylated hypoxia-inducible factor 1alpha as a mediator of p53-dependent apoptosis during hypoxia. *Oncogene*. 2001; 20:5779-5788.
335. Bae SH, Jeong JW, Park JA, *et al.* Sumoylation increases HIF-1alpha stability and its transcriptional activity. *Biochem Biophys Res Commun*. 2004; 324:394-400.
336. Berta MA, Mazure N, Hattab M, Pouyssegur J, Brahimi-Horn MC. SUMOylation of hypoxia-inducible factor-1alpha reduces its transcriptional activity. *Biochem Biophys Res Commun*. 2007; 360:646-652.
337. Tojo M, Matsuzaki K, Minami T, *et al.* The aryl hydrocarbon receptor nuclear transporter is modulated by the SUMO-1 conjugation system. *J Biol Chem*. 2002; 277:46576-46585.
338. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *N Engl J Med*. 1996; 335:865-875.

339. Blagosklonny MV, An WG, Romanova LY, Trepel J, Fojo T, Neckers L. p53 inhibits hypoxia-inducible factor-stimulated transcription. *J Biol Chem.* 1998; 273:11995-11998.
340. Zundel W, Schindler C, Haas-Kogan D, *et al.* Loss of PTEN facilitates HIF-1-mediated gene expression. *Genes Dev.* 2000; 14:391-396.
341. Zhong H, Chiles K, Feldser D, *et al.* Modulation of hypoxia-inducible factor 1alpha expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics. *Cancer Res.* 2000; 60:1541-1545.
342. Feldser D, Agani F, Iyer NV, Pak B, Ferreira G, Semenza GL. Reciprocal positive regulation of hypoxia-inducible factor 1alpha and insulin-like growth factor 2. *Cancer Res.* 1999; 59:3915-3918.
343. Richard DE, Berra E, Pouyssegur J. Nonhypoxic pathway mediates the induction of hypoxia-inducible factor 1alpha in vascular smooth muscle cells. *J Biol Chem.* 2000; 275:26765-26771.
344. Gorlach A, Diebold I, Schini-Kerth VB, *et al.* Thrombin activates the hypoxia-inducible factor-1 signaling pathway in vascular smooth muscle cells: Role of the p22(phox)-containing NADPH oxidase. *Circ Res.* 2001; 89:47-54.
345. Hellwig-Burgel T, Rutkowski K, Metzen E, Fandrey J, Jelkmann W. Interleukin-1beta and tumor necrosis factor-alpha stimulate DNA binding of hypoxia-inducible factor-1. *Blood.* 1999; 94:1561-1567.
346. Dery MA, Michaud MD, Richard DE. Hypoxia-inducible factor 1: regulation by hypoxic and non-hypoxic activators. *Int J Biochem Cell Biol.* 2005; 37:535-540.
347. Graeber TG, Osmanian C, Jacks T, *et al.* Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours. *Nature.* 1996; 379:88-91.
348. Hockel M, Schlenger K, Hockel S, Vaupel P. Hypoxic cervical cancers with low apoptotic index are highly aggressive. *Cancer Res.* 1999; 59:4525-4528.
349. Zhong H, De Marzo AM, Laughner E, *et al.* Overexpression of hypoxia-inducible factor 1alpha in common human cancers and their metastases. *Cancer Res.* 1999; 59:5830-5835.
350. Zagzag D, Zhong H, Scalzitti JM, Laughner E, Simons JW, Semenza GL. Expression of hypoxia-inducible factor 1alpha in brain tumors: association with angiogenesis, invasion, and progression. *Cancer.* 2000; 88:2606-2618.
351. Volm M, Koomagi R. Hypoxia-inducible factor (HIF-1) and its relationship to apoptosis and proliferation in lung cancer. *Anticancer Res.* 2000; 20:1527-1533.
352. Bos R, Zhong H, Hanrahan CF, *et al.* Levels of hypoxia-inducible factor-1 alpha during breast carcinogenesis. *J Natl Cancer Inst.* 2001; 93:309-314.
353. Turner KJ, Moore JW, Jones A, *et al.* Expression of hypoxia-inducible factors in human renal cancer: relationship to angiogenesis and to the von Hippel-Lindau gene mutation. *Cancer Res.* 2002; 62:2957-2961.
354. Giatromanolaki A, Koukourakis MI, Sivridis E, *et al.* Relation of hypoxia inducible factor 1 alpha and 2 alpha in operable non-small cell lung cancer to angiogenic/molecular profile of tumours and survival. *Br J Cancer.* 2001; 85:881-890.
355. Birner P, Gatterbauer B, Oberhuber G, *et al.* Expression of hypoxia-inducible factor-1 alpha in oligodendrogiomas: its impact on prognosis and on neoangiogenesis. *Cancer.* 2001; 92:165-171.
356. Bos R, van der Groep P, Greijer AE, *et al.* Levels of hypoxia-inducible factor-1alpha independently predict prognosis in patients with lymph node negative breast carcinoma. *Cancer.* 2003; 97:1573-1581.

357. Nakanishi K, Hiroi S, Tominaga S, *et al.* Expression of hypoxia-inducible factor-1alpha protein predicts survival in patients with transitional cell carcinoma of the upper urinary tract. *Clin Cancer Res.* 2005; 11:2583-2590.
358. Shibaji T, Nagao M, Ikeda N, *et al.* Prognostic significance of HIF-1 alpha overexpression in human pancreatic cancer. *Anticancer Res.* 2003; 23:4721-4727.
359. Theodoropoulos VE, Lazaris A, Sofras F, *et al.* Hypoxia-inducible factor 1 alpha expression correlates with angiogenesis and unfavorable prognosis in bladder cancer. *Eur Urol.* 2004; 46:200-208.
360. Yang QC, Zeng BF, Dong Y, Shi ZM, Jiang ZM, Huang J. Overexpression of hypoxia-inducible factor-1alpha in human osteosarcoma: correlation with clinicopathological parameters and survival outcome. *Jpn J Clin Oncol.* 2007; 37:127-134.
361. Bruick RK. Expression of the gene encoding the proapoptotic Nip3 protein is induced by hypoxia. *Proc Natl Acad Sci U S A.* 2000; 97:9082-9087.
362. Guo K, Searfoss G, Krolikowski D, *et al.* Hypoxia induces the expression of the pro-apoptotic gene BNIP3. *Cell Death Differ.* 2001; 8:367-376.
363. Shoshani T, Faerman A, Mett I, *et al.* Identification of a novel hypoxia-inducible factor 1-responsive gene, RTP801, involved in apoptosis. *Mol Cell Biol.* 2002; 22:2283-2293.
364. Blouw B, Song H, Tihan T, *et al.* The hypoxic response of tumors is dependent on their microenvironment. *Cancer Cell.* 2003; 4:133-146.
365. Carmeliet P, Dor Y, Herbert JM, *et al.* Role of HIF-1alpha in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. *Nature.* 1998; 394:485-490.
366. Pennathur-Das R, Levitt L. Augmentation of in vitro human marrow erythropoiesis under physiological oxygen tensions is mediated by monocytes and T lymphocytes. *Blood.* 1987; 69:899-907.
367. Danet GH, Pan Y, Luongo JL, Bonnet DA, Simon MC. Expansion of human SCID-repopulating cells under hypoxic conditions. *J Clin Invest.* 2003; 112:126-135.
368. Asosingh K, De Raeve H, de Ridder M, *et al.* Role of the hypoxic bone marrow microenvironment in 5T2MM murine myeloma tumor progression. *Haematologica.* 2005; 90:810-817.
369. Banai S, Shweiki D, Pinson A, Chandra M, Lazarovici G, Keshet E. Upregulation of vascular endothelial growth factor expression induced by myocardial ischaemia: implications for coronary angiogenesis. *Cardiovasc Res.* 1994; 28:1176-1179.
370. Ladoux A, Frelin C. Hypoxia is a strong inducer of vascular endothelial growth factor mRNA expression in the heart. *Biochem Biophys Res Commun.* 1993; 195:1005-1010.
371. Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature.* 1992; 359:843-845.
372. Faller DV. Endothelial cell responses to hypoxic stress. *Clin Exp Pharmacol Physiol.* 1999; 26:74-84.
373. Levy AP, Levy NS, Wegner S, Goldberg MA. Transcriptional regulation of the rat vascular endothelial growth factor gene by hypoxia. *J Biol Chem.* 1995; 270:13333-13340.
374. Liu Y, Cox SR, Morita T, Kourembanas S. Hypoxia regulates vascular endothelial growth factor gene expression in endothelial cells. Identification of a 5' enhancer. *Circ Res.* 1995; 77:638-643.
375. Mandriota SJ, Pepper MS. Regulation of angiopoietin-2 mRNA levels in bovine microvascular endothelial cells by cytokines and hypoxia. *Circ Res.* 1998; 83:852-859.

376. Mandriota SJ, Pyke C, Di Sanza C, Quinodoz P, Pittet B, Pepper MS. Hypoxia-inducible angiopoietin-2 expression is mimicked by iodonium compounds and occurs in the rat brain and skin in response to systemic hypoxia and tissue ischemia. *Am J Pathol.* 2000; 156:2077-2089.
377. Kuwabara K, Ogawa S, Matsumoto M, *et al.* Hypoxia-mediated induction of acidic/basic fibroblast growth factor and platelet-derived growth factor in mononuclear phagocytes stimulates growth of hypoxic endothelial cells. *Proc Natl Acad Sci U S A.* 1995; 92:4606-4610.
378. Kourembanas S, Hannan RL, Fallar DV. Oxygen tension regulates the expression of the platelet-derived growth factor-B chain gene in human endothelial cells. *J Clin Invest.* 1990; 86:670-674.
379. Hu J, Discher DJ, Bishopric NH, Webster KA. Hypoxia regulates expression of the endothelin-1 gene through a proximal hypoxia-inducible factor-1 binding site on the antisense strand. *Biochem Biophys Res Commun.* 1998; 245:894-899.
380. Scannell G, Waxman K, Kaml GJ, *et al.* Hypoxia induces a human macrophage cell line to release tumor necrosis factor-alpha and its soluble receptors in vitro. *J Surg Res.* 1993; 54:281-285.
381. Ambrosini G, Nath AK, Sierra-Honigmann MR, Flores-Riveros J. Transcriptional activation of the human leptin gene in response to hypoxia. Involvement of hypoxia-inducible factor 1. *J Biol Chem.* 2002; 277:34601-34609.
382. Grosfeld A, Turban S, Andre J, *et al.* Transcriptional effect of hypoxia on placental leptin. *FEBS Lett.* 2001; 502:122-126.
383. Gerber HP, Condorelli F, Park J, Ferrara N. Differential transcriptional regulation of the two vascular endothelial growth factor receptor genes. Flt-1, but not Flk-1/KDR, is up-regulated by hypoxia. *J Biol Chem.* 1997; 272:23659-23667.
384. Willam C, Koehne P, Jurgensen JS, *et al.* Tie2 receptor expression is stimulated by hypoxia and proinflammatory cytokines in human endothelial cells. *Circ Res.* 2000; 87:370-377.
385. Yuan HT, Yang SP, Woolf AS. Hypoxia up-regulates angiopoietin-2, a Tie-2 ligand, in mouse mesangial cells. *Kidney Int.* 2000; 58:1912-1919.
386. Wang T, Niki T, Goto A, *et al.* Hypoxia increases the motility of lung adenocarcinoma cell line A549 via activation of the epidermal growth factor receptor pathway. *Cancer Sci.* 2007; 98:506-511.
387. Hitchon C, Wong K, Ma G, Reed J, Lytle D, El-Gabalawy H. Hypoxia-induced production of stromal cell-derived factor 1 (CXCL12) and vascular endothelial growth factor by synovial fibroblasts. *Arthritis Rheum.* 2002; 46:2587-2597.
388. Lima e Silva R, Shen J, Hackett SF, *et al.* The SDF-1/CXCR4 ligand/receptor pair is an important contributor to several types of ocular neovascularization. *Faseb J.* 2007; 21:3219-3230.
389. Zagzag D, Krishnamachary B, Yee H, *et al.* Stromal cell-derived factor-1alpha and CXCR4 expression in hemangioblastoma and clear cell-renal cell carcinoma: von Hippel-Lindau loss-of-function induces expression of a ligand and its receptor. *Cancer Res.* 2005; 65:6178-6188.
390. Stockwin LH, Blonder J, Bumke MA, *et al.* Proteomic analysis of plasma membrane from hypoxia-adapted malignant melanoma. *J Proteome Res.* 2006; 5:2996-3007.
391. Tabatabai G, Frank B, Mohle R, Weller M, Wick W. Irradiation and hypoxia promote homing of haematopoietic progenitor cells towards gliomas by TGF-beta-dependent HIF-1alpha-mediated induction of CXCL12. *Brain.* 2006; 129:2426-2435.
392. Elvidge GP, Glenny L, Appelhoff RJ, Ratcliffe PJ, Ragoussis J, Gleadle JM. Concordant regulation of gene expression by hypoxia and 2-oxoglutarate-dependent

- dioxygenase inhibition: the role of HIF-1alpha, HIF-2alpha, and other pathways. *J Biol Chem.* 2006; 281:15215-15226.
- 393. Staller P, Sulitkova J, Lisztwan J, Moch H, Oakeley EJ, Krek W. Chemokine receptor CXCR4 downregulated by von Hippel-Lindau tumour suppressor pVHL. *Nature.* 2003; 425:307-311.
  - 394. Schioppa T, Uranchimeg B, Saccani A, *et al.* Regulation of the chemokine receptor CXCR4 by hypoxia. *J Exp Med.* 2003; 198:1391-1402.
  - 395. Scheurer SB, Raybak JN, Rosli C, Neri D, Elia G. Modulation of gene expression by hypoxia in human umbilical cord vein endothelial cells: A transcriptomic and proteomic study (vol. 4, Issue 6, pp. 1737-1760). *Proteomics.* 2004; 4:2822.
  - 396. Pan J, Mestas J, Burdick MD, *et al.* Stromal derived factor-1 (SDF-1/CXCL12) and CXCR4 in renal cell carcinoma metastasis. *Mol Cancer.* 2006; 5:56.
  - 397. Zagzag D, Lukyanov Y, Lan L, *et al.* Hypoxia-inducible factor 1 and VEGF upregulate CXCR4 in glioblastoma: implications for angiogenesis and glioma cell invasion. *Lab Invest.* 2006; 86:1221-1232.
  - 398. Zagzag D, Esencay M, Mendez O, *et al.* Hypoxia- and vascular endothelial growth factor-induced stromal cell-derived factor-1alpha/CXCR4 expression in glioblastomas: one plausible explanation of Scherer's structures. *Am J Pathol.* 2008; 173:545-560.
  - 399. Irigoyen M, Anso E, Martinez E, Garayoa M, Martinez-Irujo JJ, Rouzaut A. Hypoxia alters the adhesive properties of lymphatic endothelial cells. A transcriptional and functional study. *Biochim Biophys Acta.* 2007; 1773:880-890.
  - 400. Piovan E, Tosello V, Indraccolo S, *et al.* Differential regulation of hypoxia-induced CXCR4 triggering during B-cell development and lymphomagenesis. *Cancer Res.* 2007; 67:8605-8614.
  - 401. Wang X, Li C, Chen Y, *et al.* Hypoxia enhances CXCR4 expression favoring microglia migration via HIF-1alpha activation. *Biochem Biophys Res Commun.* 2008; 371:283-288.
  - 402. Hung SC, Pochampally RR, Hsu SC, *et al.* Short-term exposure of multipotent stromal cells to low oxygen increases their expression of CX3CR1 and CXCR4 and their engraftment in vivo. *PLoS ONE.* 2007; 2:e416.
  - 403. Liu YL, Yu JM, Song XR, Wang XW, Xing LG, Gao BB. Regulation of the chemokine receptor CXCR4 and metastasis by hypoxia-inducible factor in non small cell lung cancer cell lines. *Cancer Biol Ther.* 2006; 5:1320-1326.
  - 404. Rajkumar SV, Hayman S, Gertz MA, *et al.* Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol.* 2002; 20:4319-4323.
  - 405. Sezer O, Niemoller K, Eucker J, *et al.* Bone marrow microvessel density is a prognostic factor for survival in patients with multiple myeloma. *Ann Hematol.* 2000; 79:574-577.
  - 406. Weidner N, Semple JP, Welch WR, Folkman J. Tumor angiogenesis and metastasis--correlation in invasive breast carcinoma. *N Engl J Med.* 1991; 324:1-8.
  - 407. Laroche M, Brousset P, Ludot I, Mazieres B, Thiechart M, Attal M. Increased vascularization in myeloma. *Eur J Haematol.* 2001; 66:89-93.
  - 408. Ribatti D, Vacca A, Nico B, *et al.* Bone marrow angiogenesis and mast cell density increase simultaneously with progression of human multiple myeloma. *Br J Cancer.* 1999; 79:451-455.
  - 409. Sambrook J, Fritsch EF, Maniatis J. Molecular Cloning: A Laboratory Manual. 1989.
  - 410. Maniatis T, Fritsch EF, Sambrook J. Molecular cloning: A Laboratory Manual; 1982.

411. Ponomarev V, Doubrovin M, Serganova I, *et al.* A novel triple-modality reporter gene for whole-body fluorescent, bioluminescent, and nuclear noninvasive imaging. *Eur J Nucl Med Mol Imaging*. 2004; 31:740-751.
412. Vacca A, Ribatti D, Roccaro AM, Ria R, Palermo L, Dammacco F. Bone marrow angiogenesis and plasma cell angiogenic and invasive potential in patients with active multiple myeloma. *Acta Haematol*. 2001; 106:162-169.
413. Rajkumar SV, Mesa RA, Fonseca R, *et al.* Bone marrow angiogenesis in 400 patients with monoclonal gammopathy of undetermined significance, multiple myeloma, and primary amyloidosis. *Clin Cancer Res*. 2002; 8:2210-2216.
414. Strieter RM, Polverini PJ, Arenberg DA, Kunkel SL. The role of CXC chemokines as regulators of angiogenesis. *Shock*. 1995; 4:155-160.
415. Ponomaryov T, Peled A, Petit I, *et al.* Induction of the chemokine stromal-derived factor-1 following DNA damage improves human stem cell function. *J Clin Invest*. 2000; 106:1331-1339.
416. Sun YX, Schneider A, Jung Y, *et al.* Skeletal localization and neutralization of the SDF-1(CXCL12)/CXCR4 axis blocks prostate cancer metastasis and growth in osseous sites *in vivo*. *J Bone Miner Res*. 2005; 20:318-329.
417. Kim YM, Lee YM, Kim HS, *et al.* TNF-related activation-induced cytokine (TRANCE) induces angiogenesis through the activation of Src and phospholipase C (PLC) in human endothelial cells. *J Biol Chem*. 2002; 277:6799-6805.
418. Min JK, Kim YM, Kim EC, *et al.* Vascular endothelial growth factor up-regulates expression of receptor activator of NF-kappa B (RANK) in endothelial cells. Concomitant increase of angiogenic responses to RANK ligand. *J Biol Chem*. 2003; 278:39548-39557.
419. Rafii S, Shapiro F, Rimarachin J, *et al.* Isolation and characterization of human bone marrow microvascular endothelial cells: hematopoietic progenitor cell adhesion. *Blood*. 1994; 84:10-19.
420. Schweitzer KM, Vicart P, Delouis C, *et al.* Characterization of a newly established human bone marrow endothelial cell line: distinct adhesive properties for hematopoietic progenitors compared with human umbilical vein endothelial cells. *Lab Invest*. 1997; 76:25-36.
421. Hasan J, Byers R, Jayson GC. Intra-tumoural microvessel density in human solid tumours. *Br J Cancer*. 2002; 86:1566-1577.
422. Hlatky L, Hahnfeldt P, Folkman J. Clinical application of antiangiogenic therapy: microvessel density, what it does and doesn't tell us. *J Natl Cancer Inst*. 2002; 94:883-893.
423. De Raeve HR, Vermeulen PB, Vanderkerken K, Harris AL, Van Marck E. Microvessel density, endothelial-cell proliferation and carbonic anhydrase IX expression in haematological malignancies, bone-marrow metastases and monoclonal gammopathy of undetermined significance. *Virchows Arch*. 2004; 445:27-35.
424. Hillyer P, Mordelet E, Flynn G, Male D. Chemokines, chemokine receptors and adhesion molecules on different human endothelia: discriminating the tissue-specific functions that affect leucocyte migration. *Clin Exp Immunol*. 2003; 134:431-441.
425. Yun HJ, Jo DY. Production of stromal cell-derived factor-1 (SDF-1) and expression of CXCR4 in human bone marrow endothelial cells. *J Korean Med Sci*. 2003; 18:679-685.
426. Hendrix CW, Flexner C, MacFarland RT, *et al.* Pharmacokinetics and safety of AMD-3100, a novel antagonist of the CXCR-4 chemokine receptor, in human volunteers. *Antimicrob Agents Chemother*. 2000; 44:1667-1673.

427. Matthys P, Hatse S, Vermeire K, *et al.* AMD3100, a potent and specific antagonist of the stromal cell-derived factor-1 chemokine receptor CXCR4, inhibits autoimmune joint inflammation in IFN-gamma receptor-deficient mice. *J Immunol.* 2001; 167:4686-4692.
428. Hatse S, Princen K, Bridger G, De Clercq E, Schols D. Chemokine receptor inhibition by AMD3100 is strictly confined to CXCR4. *FEBS Lett.* 2002; 527:255-262.
429. Arakaki R, Tamamura H, Premanathan M, *et al.* T134, a small-molecule CXCR4 inhibitor, has no cross-drug resistance with AMD3100, a CXCR4 antagonist with a different structure. *J Virol.* 1999; 73:1719-1723.
430. Tamamura H, Xu Y, Hattori T, *et al.* A low-molecular-weight inhibitor against the chemokine receptor CXCR4: a strong anti-HIV peptide T140. *Biochem Biophys Res Commun.* 1998; 253:877-882.
431. Takenaga M, Tamamura H, Hiramatsu K, *et al.* A single treatment with microcapsules containing a CXCR4 antagonist suppresses pulmonary metastasis of murine melanoma. *Biochem Biophys Res Commun.* 2004; 320:226-232.
432. Tamamura H, Hori A, Kanzaki N, *et al.* T140 analogs as CXCR4 antagonists identified as anti-metastatic agents in the treatment of breast cancer. *FEBS Lett.* 2003; 550:79-83.
433. Burger M, Hartmann T, Krome M, *et al.* Small peptide inhibitors of the CXCR4 chemokine receptor (CD184) antagonize the activation, migration, and antiapoptotic responses of CXCL12 in chronic lymphocytic leukemia B cells. *Blood.* 2005; 106:1824-1830.
434. Juarez J, Bradstock KF, Gottlieb DJ, Bendall LJ. Effects of inhibitors of the chemokine receptor CXCR4 on acute lymphoblastic leukemia cells in vitro. *Leukemia.* 2003; 17:1294-1300.
435. Libura J, Drukala J, Majka M, *et al.* CXCR4-SDF-1 signaling is active in rhabdomyosarcoma cells and regulates locomotion, chemotaxis, and adhesion. *Blood.* 2002; 100:2597-2606.
436. Tamamura H, Fujisawa M, Hiramatsu K, *et al.* Identification of a CXCR4 antagonist, a T140 analog, as an anti-rheumatoid arthritis agent. *FEBS Lett.* 2004; 569:99-104.
437. Brahimi-Horn MC, Pouyssegur J. Harnessing the hypoxia-inducible factor in cancer and ischemic disease. *Biochem Pharmacol.* 2007; 73:450-457.
438. Harris AL. Hypoxia--a key regulatory factor in tumour growth. *Nat Rev Cancer.* 2002; 2:38-47.
439. O'Rourke JF, Tian YM, Ratcliffe PJ, Pugh CW. Oxygen-regulated and transactivating domains in endothelial PAS protein 1: comparison with hypoxia-inducible factor-1alpha. *J Biol Chem.* 1999; 274:2060-2071.
440. Berra E, Richard DE, Gothe E, Pouyssegur J. HIF-1-dependent transcriptional activity is required for oxygen-mediated HIF-1alpha degradation. *FEBS Lett.* 2001; 491:85-90.
441. Hu CJ, Iyer S, Sataur A, Covello KL, Chodosh LA, Simon MC. Differential regulation of the transcriptional activities of hypoxia-inducible factor 1 alpha (HIF-1alpha) and HIF-2alpha in stem cells. *Mol Cell Biol.* 2006; 26:3514-3526.
442. Brown JM, Wilson WR. Exploiting tumour hypoxia in cancer treatment. *Nat Rev Cancer.* 2004; 4:437-447.
443. Goda F, O'Hara JA, Liu KJ, Rhodes ES, Dunn JF, Swartz HM. Comparisons of measurements of pO<sub>2</sub> in tissue in vivo by EPR oximetry and microelectrodes. *Adv Exp Med Biol.* 1997; 411:543-549.

444. Evens AM, Schumacker PT, Helenowski IB, *et al.* Hypoxia inducible factor-alpha activation in lymphoma and relationship to the thioredoxin family. *Br J Haematol*. 2008; 141:676-680.
445. Giatromanolaki A, Koukourakis MI, Pezzella F, *et al.* Phosphorylated VEGFR2/KDR receptors are widely expressed in B-cell non-Hodgkin's lymphomas and correlate with hypoxia inducible factor activation. *Hematol Oncol*. 2008.
446. Frater JL, Kay NE, Goolsby CL, Crawford SE, Dewald GW, Peterson LC. Dysregulated angiogenesis in B-chronic lymphocytic leukemia: Morphologic, immunohistochemical, and flow cytometric evidence. *Diagn Pathol*. 2008; 3:16.
447. Wellmann S, Guschmann M, Griethe W, *et al.* Activation of the HIF pathway in childhood ALL, prognostic implications of VEGF. *Leukemia*. 2004; 18:926-933.
448. Ebert BL, Firth JD, Ratcliffe PJ. Hypoxia and mitochondrial inhibitors regulate expression of glucose transporter-1 via distinct Cis-acting sequences. *J Biol Chem*. 1995; 270:29083-29089.
449. Sivitz WI, Lund DD, Yorek B, Grover-McKay M, Schmid PG. Pretranslational regulation of two cardiac glucose transporters in rats exposed to hypobaric hypoxia. *Am J Physiol*. 1992; 263:E562-569.
450. Chakrabarti J, Turley H, Campo L, *et al.* The transcription factor DEC1 (stra13, SHARP2) is associated with the hypoxic response and high tumour grade in human breast cancers. *Br J Cancer*. 2004; 91:954-958.
451. Ivanova AV, Ivanov SV, Danilkovitch-Miagkova A, Lerman MI. Regulation of STRA13 by the von Hippel-Lindau tumor suppressor protein, hypoxia, and the UBC9/ubiquitin proteasome degradation pathway. *J Biol Chem*. 2001; 276:15306-15315.
452. Miyazaki K, Kawamoto T, Tanimoto K, Nishiyama M, Honda H, Kato Y. Identification of functional hypoxia response elements in the promoter region of the DEC1 and DEC2 genes. *J Biol Chem*. 2002; 277:47014-47021.
453. Gleadle JM, Ebert BL, Firth JD, Ratcliffe PJ. Regulation of angiogenic growth factor expression by hypoxia, transition metals, and chelating agents. *Am J Physiol*. 1995; 268:C1362-1368.
454. Goldberg MA, Schneider TJ. Similarities between the oxygen-sensing mechanisms regulating the expression of vascular endothelial growth factor and erythropoietin. *J Biol Chem*. 1994; 269:4355-4359.
455. Angst E, Sibold S, Tiffon C, *et al.* Cellular differentiation determines the expression of the hypoxia-inducible protein NDRG1 in pancreatic cancer. *Br J Cancer*. 2006; 95:307-313.
456. Cangul H. Hypoxia upregulates the expression of the NDRG1 gene leading to its overexpression in various human cancers. *BMC Genet*. 2004; 5:27.
457. Han YH, Xia L, Song LP, *et al.* Comparative proteomic analysis of hypoxia-treated and untreated human leukemic U937 cells. *Proteomics*. 2006; 6:3262-3274.
458. Carroll VA, Ashcroft M. Role of hypoxia-inducible factor (HIF)-1alpha versus HIF-2alpha in the regulation of HIF target genes in response to hypoxia, insulin-like growth factor-I, or loss of von Hippel-Lindau function: implications for targeting the HIF pathway. *Cancer Res*. 2006; 66:6264-6270.
459. Raval RR, Lau KW, Tran MG, *et al.* Contrasting properties of hypoxia-inducible factor 1 (HIF-1) and HIF-2 in von Hippel-Lindau-associated renal cell carcinoma. *Mol Cell Biol*. 2005; 25:5675-5686.
460. Hu X, Dai S, Wu WJ, *et al.* Stromal cell derived factor-1 alpha confers protection against myocardial ischemia/reperfusion injury: role of the cardiac stromal cell derived factor-1 alpha CXCR4 axis. *Circulation*. 2007; 116:654-663.

461. Marxsen JH, Stengel P, Doege K, *et al.* Hypoxia-inducible factor-1 (HIF-1) promotes its degradation by induction of HIF-alpha-prolyl-4-hydroxylases. *Biochem J.* 2004; 381:761-767.
462. D'Angelo G, Duplan E, Boyer N, Vigne P, Frelin C. Hypoxia up-regulates prolyl hydroxylase activity: a feedback mechanism that limits HIF-1 responses during reoxygenation. *J Biol Chem.* 2003; 278:38183-38187.
463. Favier J, Lapointe S, Maliba R, Sirois MG. HIF2 alpha reduces growth rate but promotes angiogenesis in a mouse model of neuroblastoma. *BMC Cancer.* 2007; 7:139.
464. Wang V, Davis DA, Haque M, Huang LE, Yarchoan R. Differential gene up-regulation by hypoxia-inducible factor-1alpha and hypoxia-inducible factor-2alpha in HEK293T cells. *Cancer Res.* 2005; 65:3299-3306.
465. Warnecke C, Zaborowska Z, Kurreck J, *et al.* Differentiating the functional role of hypoxia-inducible factor (HIF)-1alpha and HIF-2alpha (EPAS-1) by the use of RNA interference: erythropoietin is a HIF-2alpha target gene in Hep3B and Kelly cells. *Faseb J.* 2004; 18:1462-1464.
466. Rankin EB, Biju MP, Liu Q, *et al.* Hypoxia-inducible factor-2 (HIF-2) regulates hepatic erythropoietin in vivo. *J Clin Invest.* 2007; 117:1068-1077.
467. Smith K, Gunaratnam L, Morley M, Franovic A, Mekhail K, Lee S. Silencing of epidermal growth factor receptor suppresses hypoxia-inducible factor-2-driven VHL-/- renal cancer. *Cancer Res.* 2005; 65:5221-5230.
468. Aprelikova O, Chandramouli GV, Wood M, *et al.* Regulation of HIF prolyl hydroxylases by hypoxia-inducible factors. *J Cell Biochem.* 2004; 92:491-501.
469. McQuibban GA, Butler GS, Gong JH, *et al.* Matrix metalloproteinase activity inactivates the CXC chemokine stromal cell-derived factor-1. *J Biol Chem.* 2001; 276:43503-43508.
470. Lambeir AM, Proost P, Durinx C, *et al.* Kinetic investigation of chemokine truncation by CD26/dipeptidyl peptidase IV reveals a striking selectivity within the chemokine family. *J Biol Chem.* 2001; 276:29839-29845.
471. Proost P, Struyf S, Schols D, *et al.* Processing by CD26/dipeptidyl-peptidase IV reduces the chemotactic and anti-HIV-1 activity of stromal-cell-derived factor-1alpha. *FEBS Lett.* 1998; 432:73-76.
472. Delgado MB, Clark-Lewis I, Loetscher P, *et al.* Rapid inactivation of stromal cell-derived factor-1 by cathepsin G associated with lymphocytes. *Eur J Immunol.* 2001; 31:699-707.
473. Valenzuela-Fernandez A, Planchenault T, Baleux F, *et al.* Leukocyte elastase negatively regulates Stromal cell-derived factor-1 (SDF-1)/CXCR4 binding and functions by amino-terminal processing of SDF-1 and CXCR4. *J Biol Chem.* 2002; 277:15677-15689.
474. Jain RK, Schlenger K, Hockel M, Yuan F. Quantitative angiogenesis assays: progress and problems. *Nat Med.* 1997; 3:1203-1208.
475. Hasan J, Shnyder SD, Bibby M, Double JA, Bicknel R, Jayson GC. Quantitative angiogenesis assays in vivo--a review. *Angiogenesis.* 2004; 7:1-16.
476. Gimbrone MA, Jr., Cotran RS, Leapman SB, Folkman J. Tumor growth and neovascularization: an experimental model using the rabbit cornea. *J Natl Cancer Inst.* 1974; 52:413-427.
477. Shirozu M, Nakano T, Inazawa J, *et al.* Structure and chromosomal localization of the human stromal cell-derived factor 1 (SDF1) gene. *Genomics.* 1995; 28:495-500.
478. Guleng B, Tateishi K, Ohta M, *et al.* Blockade of the stromal cell-derived factor-1/CXCR4 axis attenuates in vivo tumor growth by inhibiting angiogenesis in a

- vascular endothelial growth factor-independent manner. *Cancer Res.* 2005; 65:5864-5871.
- 479. Liang Z, Brooks J, Willard M, *et al.* CXCR4/CXCL12 axis promotes VEGF-mediated tumor angiogenesis through Akt signaling pathway. *Biochem Biophys Res Commun.* 2007; 359:716-722.
  - 480. Kollmar O, Rupertus K, Scheuer C, *et al.* Stromal cell-derived factor-1 promotes cell migration and tumor growth of colorectal metastasis. *Neoplasia.* 2007; 9:862-870.
  - 481. Araki K, Sangai T, Miyamoto S, *et al.* Inhibition of bone-derived insulin-like growth factors by a ligand-specific antibody suppresses the growth of human multiple myeloma in the human adult bone explanted in NOD/SCID mouse. *Int J Cancer.* 2006; 118:2602-2608.
  - 482. Campbell RA, Manyak SJ, Yang HH, *et al.* LAGlambda-1: a clinically relevant drug resistant human multiple myeloma tumor murine model that enables rapid evaluation of treatments for multiple myeloma. *Int J Oncol.* 2006; 28:1409-1417.
  - 483. Radl J, Croese JW, Zurcher C, Van den Enden-Vieeën MH, de Leeuw AM. Animal model of human disease. *Multiple myeloma.* *Am J Pathol.* 1988; 132:593-597.
  - 484. Yaccoby S, Barlogie B, Epstein J. Primary myeloma cells growing in SCID-hu mice: a model for studying the biology and treatment of myeloma and its manifestations. *Blood.* 1998; 92:2908-2913.
  - 485. Van Valckenborgh E, De Raeve H, Devy L, *et al.* Murine 5T multiple myeloma cells induce angiogenesis in vitro and in vivo. *Br J Cancer.* 2002; 86:796-802.
  - 486. Ribatti D, De Falco G, Nico B, Ria R, Crivellato E, Vacca A. In vivo time-course of the angiogenic response induced by multiple myeloma plasma cells in the chick embryo chorioallantoic membrane. *J Anat.* 2003; 203:323-328.
  - 487. Podar K, Tonon G, Sattler M, *et al.* The small-molecule VEGF receptor inhibitor pazopanib (GW786034B) targets both tumor and endothelial cells in multiple myeloma. *Proc Natl Acad Sci U S A.* 2006; 103:19478-19483.
  - 488. Frost P, Moatamed F, Hoang B, *et al.* In vivo antitumor effects of the mTOR inhibitor CCI-779 against human multiple myeloma cells in a xenograft model. *Blood.* 2004; 104:4181-4187.
  - 489. Podar K, Raab MS, Zhang J, *et al.* Targeting PKC in multiple myeloma: in vitro and in vivo effects of the novel, orally available small-molecule inhibitor enzastaurin (LY317615.HCl). *Blood.* 2007; 109:1669-1677.
  - 490. Sawaoka H, Kawano S, Tsuji S, *et al.* Cyclooxygenase-2 inhibitors suppress the growth of gastric cancer xenografts via induction of apoptosis in nude mice. *Am J Physiol.* 1998; 274:G1061-1067.
  - 491. Akhtar N, Dickerson EB, Auerbach R. The sponge/Matrigel angiogenesis assay. *Angiogenesis.* 2002; 5:75-80.
  - 492. Passaniti A, Taylor RM, Pili R, *et al.* A simple, quantitative method for assessing angiogenesis and antiangiogenic agents using reconstituted basement membrane, heparin, and fibroblast growth factor. *Lab Invest.* 1992; 67:519-528.
  - 493. Malinda K. In Vivo Matrigel Migration and Angiogenesis Assays. In: Murray JC, ed. *Methods in Molecular Medicine: Angiogenesis Protocols.* Vol. 46: Humana Press; 2001:47-52.
  - 494. Wang J, Wang J, Sun Y, *et al.* Diverse signaling pathways through the SDF-1/CXCR4 chemokine axis in prostate cancer cell lines leads to altered patterns of cytokine secretion and angiogenesis. *Cell Signal.* 2005; 17:1578-1592.
  - 495. Chu CY, Cha ST, Lin WC, *et al.* Stromal-cell-derived factor-1 $\{\alpha\}$  (SDF-1 $\{\alpha\}$ /CXCL12)-enhanced angiogenesis of human basal cell carcinoma cells involves ERK1/2-NF- $\{\kappa\}$  B/interleukin-6 pathway. *Carcinogenesis.* 2008.

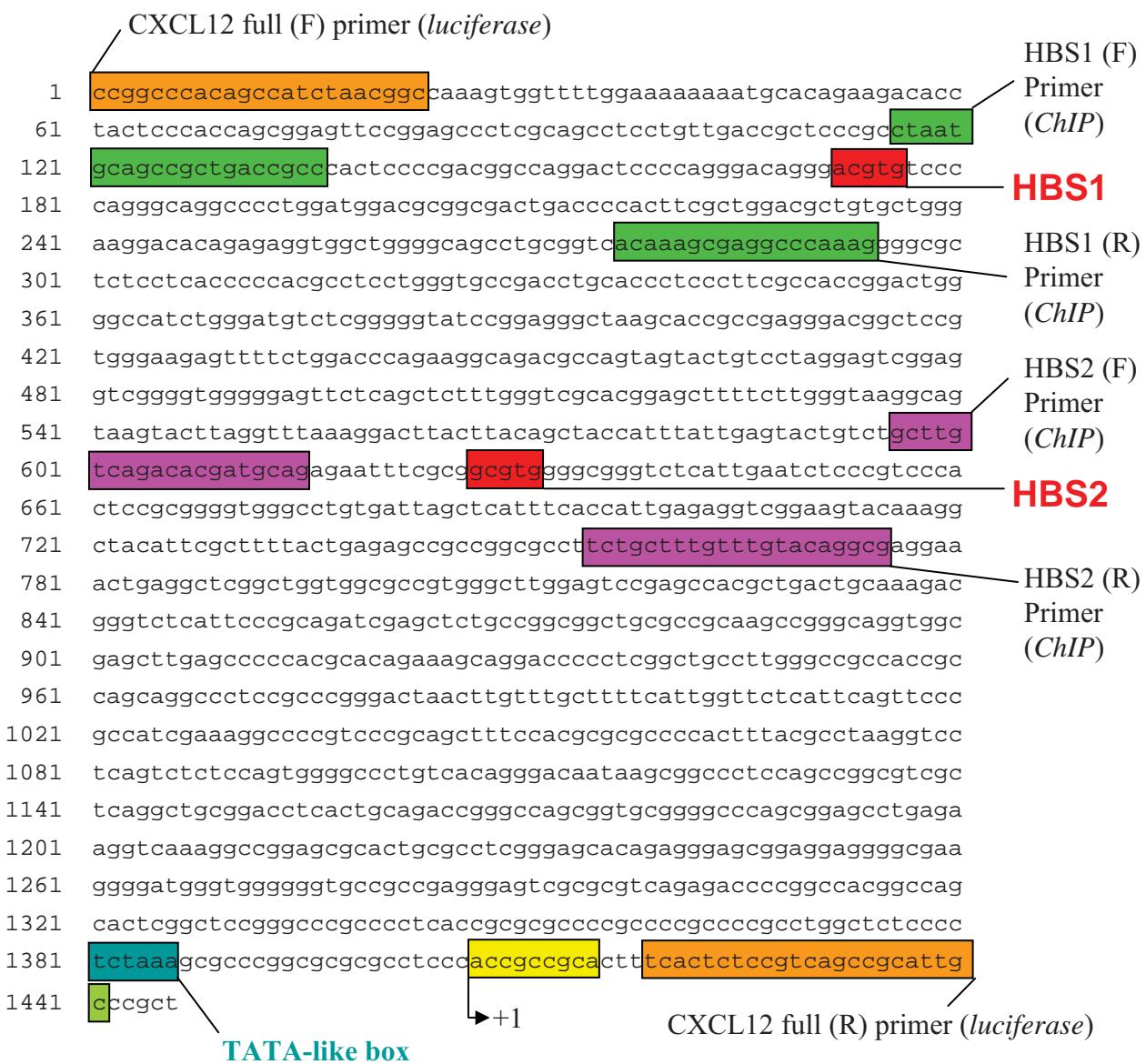
496. Ioachim E, Michael M, Salmas M, Michael MM, Stavropoulos NE, Malamou-Mitsi V. Hypoxia-inducible factors HIF-1alpha and HIF-2alpha expression in bladder cancer and their associations with other angiogenesis-related proteins. *Urol Int.* 2006; 77:255-263.
497. Yang QC, Zeng BF, Shi ZM, *et al.* Inhibition of hypoxia-induced angiogenesis by trichostatin A via suppression of HIF-1a activity in human osteosarcoma. *J Exp Clin Cancer Res.* 2006; 25:593-599.
498. Bangoura G, Liu ZS, Qian Q, Jiang CQ, Yang GF, Jing S. Prognostic significance of HIF-2alpha/EPAS1 expression in hepatocellular carcinoma. *World J Gastroenterol.* 2007; 13:3176-3182.
499. Lekas A, Lazaris AC, Deliveliotis C, *et al.* The expression of hypoxia-inducible factor-1alpha (HIF-1alpha) and angiogenesis markers in hyperplastic and malignant prostate tissue. *Anticancer Res.* 2006; 26:2989-2993.
500. Mizokami K, Kakeji Y, Oda S, *et al.* Clinicopathologic significance of hypoxia-inducible factor 1alpha overexpression in gastric carcinomas. *J Surg Oncol.* 2006; 94:149-154.
501. Yu JX, Cui L, Zhang QY, *et al.* Expression of NOS and HIF-1alpha in human colorectal carcinoma and implication in tumor angiogenesis. *World J Gastroenterol.* 2006; 12:4660-4664.
502. Kubo T, Sugita T, Shimose S, Matsuo T, Arihiro K, Ochi M. Expression of hypoxia-inducible factor-1alpha and its relationship to tumour angiogenesis and cell proliferation in cartilage tumours. *J Bone Joint Surg Br.* 2008; 90:364-370.
503. Theodoropoulos GE, Lazaris AC, Theodoropoulos VE, *et al.* Hypoxia, angiogenesis and apoptosis markers in locally advanced rectal cancer. *Int J Colorectal Dis.* 2006; 21:248-257.
504. Zhang N, Gong K, Yang XY, Xin DQ, Na YQ. [Expression of hypoxia-inducible factor-1-alpha, hypoxia-inducible factor-2alpha and vascular endothelial growth factor in sporadic clear cell renal cell renal cell carcinoma and their significance in the pathogenesis thereof]. *Zhonghua Yi Xue Za Zhi.* 2006; 86:1526-1529.
505. Sui J, Wu J, Li X, *et al.* [The expression and significance of hypoxia inducible factor-1alpha and microvessel density in human nasopharyngeal carcinoma]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* 2008; 22:269-272.
506. Birner P, Schindl M, Obermair A, Breitenecker G, Oberhuber G. Expression of hypoxia-inducible factor 1alpha in epithelial ovarian tumors: its impact on prognosis and on response to chemotherapy. *Clin Cancer Res.* 2001; 7:1661-1668.
507. Kondo Y, Hamada J, Kobayashi C, *et al.* Over expression of hypoxia-inducible factor-1alpha in renal and bladder cancer cells increases tumorigenic potency. *J Urol.* 2005; 173:1762-1766.
508. Maranchie JK, Vasselli JR, Riss J, Bonifacino JS, Linehan WM, Klausner RD. The contribution of VHL substrate binding and HIF1-alpha to the phenotype of VHL loss in renal cell carcinoma. *Cancer Cell.* 2002; 1:247-255.
509. Ravi R, Mookerjee B, Bhujwalla ZM, *et al.* Regulation of tumor angiogenesis by p53-induced degradation of hypoxia-inducible factor 1alpha. *Genes Dev.* 2000; 14:34-44.
510. Blancher C, Moore JW, Talks KL, Houlbrook S, Harris AL. Relationship of hypoxia-inducible factor (HIF)-1alpha and HIF-2alpha expression to vascular endothelial growth factor induction and hypoxia survival in human breast cancer cell lines. *Cancer Res.* 2000; 60:7106-7113.
511. Ria R, Roccaro AM, Merchionne F, Vacca A, Dammacco F, Ribatti D. Vascular endothelial growth factor and its receptors in multiple myeloma. *Leukemia.* 2003; 17:1961-1966.

512. Alexandrakis MG, Passam FJ, Ganotakis E, *et al.* Bone marrow microvascular density and angiogenic growth factors in multiple myeloma. *Clin Chem Lab Med.* 2004; 42:1122-1126.
513. Andersen NF, Standal T, Nielsen JL, *et al.* Syndecan-1 and angiogenic cytokines in multiple myeloma: correlation with bone marrow angiogenesis and survival. *Br J Haematol.* 2005; 128:210-217.
514. Iwasaki T, Hamano T, Ogata A, Hashimoto N, Kitano M, Kakishita E. Clinical significance of vascular endothelial growth factor and hepatocyte growth factor in multiple myeloma. *Br J Haematol.* 2002; 116:796-802.
515. Seidel C, Borset M, Turesson I, Abildgaard N, Sundan A, Waage A. Elevated serum concentrations of hepatocyte growth factor in patients with multiple myeloma. The Nordic Myeloma Study Group. *Blood.* 1998; 91:806-812.
516. Vacca A, Ria R, Ribatti D, *et al.* A paracrine loop in the vascular endothelial growth factor pathway triggers tumor angiogenesis and growth in multiple myeloma. *Haematologica.* 2003; 88:176-185.
517. Oh JW, Drabik K, Kutsch O, Choi C, Tousson A, Benveniste EN. CXC chemokine receptor 4 expression and function in human astrogloma cells. *J Immunol.* 2001; 166:2695-2704.
518. Ping YF, Yao XH, Chen JH, *et al.* The anti-cancer compound Nordy inhibits CXCR4-mediated production of IL-8 and VEGF by malignant human glioma cells. *J Neurooncol.* 2007; 84:21-29.
519. Yang SX, Chen JH, Jiang XF, *et al.* Activation of chemokine receptor CXCR4 in malignant glioma cells promotes the production of vascular endothelial growth factor. *Biochem Biophys Res Commun.* 2005; 335:523-528.
520. Zhang H, Vakil V, Braunstein M, *et al.* Circulating endothelial progenitor cells in multiple myeloma: implications and significance. *Blood.* 2005; 105:3286-3294.
521. Hattori K, Heissig B, Tashiro K, *et al.* Plasma elevation of stromal cell-derived factor-1 induces mobilization of mature and immature hematopoietic progenitor and stem cells. *Blood.* 2001; 97:3354-3360.
522. Heissig B, Hattori K, Dias S, *et al.* Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand. *Cell.* 2002; 109:625-637.
523. Aghi M, Cohen KS, Klein RJ, Scadden DT, Chiocca EA. Tumor stromal-derived factor-1 recruits vascular progenitors to mitotic neovasculature, where microenvironment influences their differentiated phenotypes. *Cancer Res.* 2006; 66:9054-9064.
524. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. *Clin Ther.* 2006; 28:1779-1802.
525. Khosravi Shahi P, Fernandez Pineda I. Tumoral angiogenesis: review of the literature. *Cancer Invest.* 2008; 26:104-108.
526. Dal Lago L, D'Hondt V, Awada A. Selected combination therapy with sorafenib: a review of clinical data and perspectives in advanced solid tumors. *Oncologist.* 2008; 13:845-858.
527. Faber A, Roderburg C, Wein F, *et al.* The Many Facets of SDF-1alpha, CXCR4 Agonists and Antagonists on Hematopoietic Progenitor Cells. *J Biomed Biotechnol.* 2007; 2007:26065.
528. Kim SY, Lee CH, Midura BV, *et al.* Inhibition of the CXCR4/CXCL12 chemokine pathway reduces the development of murine pulmonary metastases. *Clin Exp Metastasis.* 2008; 25:201-211.

529. Jin DK, Shido K, Kopp HG, *et al.* Cytokine-mediated deployment of SDF-1 induces revascularization through recruitment of CXCR4<sup>+</sup> hemangiocytes. *Nat Med.* 2006; 12:557-567.
530. Grunewald M, Avraham I, Dor Y, *et al.* VEGF-induced adult neovascularization: recruitment, retention, and role of accessory cells. *Cell.* 2006; 124:175-189.
531. Carr AN, Howard BW, Yang HT, *et al.* Efficacy of systemic administration of SDF-1 in a model of vascular insufficiency: support for an endothelium-dependent mechanism. *Cardiovasc Res.* 2006; 69:925-935.
532. Petit I, Jin D, Rafii S. The SDF-1-CXCR4 signaling pathway: a molecular hub modulating neo-angiogenesis. *Trends Immunol.* 2007; 28:299-307.
533. Bottaro DP, Liotta LA. Cancer: Out of air is not out of action. *Nature.* 2003; 423:593-595.
534. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med.* 2001; 7:987-989.
535. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science.* 2005; 307:58-62.
536. Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004; 350:2335-2342.
537. Mueller MM. Inflammation and Angiogenesis: Innate Immune Cells as Modulators of Tumor Vascularisation. *Tumor Angiogenesis:* Springer Berlin Heidelberg; 2008:351-362.
538. Alici E, Konstantinidis KV, Aints A, Dilber MS, Abedi-Valugerdi M. Visualization of 5T33 myeloma cells in the C57BL/KaLwRij mouse: establishment of a new syngeneic murine model of multiple myeloma. *Exp Hematol.* 2004; 32:1064-1072.
539. Asosingh K, Radl J, Van Riet I, Van Camp B, Vanderkerken K. The 5TMM series: a useful *in vivo* mouse model of human multiple myeloma. *Hematol J.* 2000; 1:351-356.
540. Manning LS, Berger JD, O'Donoghue HL, Sheridan GN, Claringbold PG, Turner JH. A model of multiple myeloma: culture of 5T33 murine myeloma cells and evaluation of tumorigenicity in the C57BL/KaLwRij mouse. *Br J Cancer.* 1992; 66:1088-1093.
541. Radl J, Hollander CF, van den Berg P, de Groot E. Idiopathic paraproteinaemia. I. Studies in an animal model--the ageing C57BL/KaLwRij mouse. *Clin Exp Immunol.* 1978; 33:395-402.
542. Radl J, Punt YA, van den Enden-Vieeën MH, *et al.* The 5T mouse multiple myeloma model: absence of c-myc oncogene rearrangement in early transplant generations. *Br J Cancer.* 1990; 61:276-278.
543. Edwards CM, Edwards JR, Lwin ST, *et al.* Increasing Wnt signaling in the bone marrow microenvironment inhibits the development of myeloma bone disease and reduces tumor burden in bone *in vivo*. *Blood.* 2008; 111:2833-2842.
544. Oyajobi BO, Munoz S, Kakonen R, *et al.* Detection of myeloma in skeleton of mice by whole-body optical fluorescence imaging. *Mol Cancer Ther.* 2007; 6:1701-1708.
545. Goel A, Carlson SK, Classic KL, *et al.* Radioiodide imaging and radiotherapy of multiple myeloma using VSV(Delta51)-NIS, an attenuated vesicular stomatitis virus encoding the sodium iodide symporter gene. *Blood.* 2007; 110:2342-2350.
546. Goel A, Dispenzieri A, Geyer SM, Greiner S, Peng KW, Russell SJ. Synergistic activity of the proteasome inhibitor PS-341 with non-myeloablative 153-Sm-EDTMP skeletally targeted radiotherapy in an orthotopic model of multiple myeloma. *Blood.* 2006; 107:4063-4070.

547. Wang S, Yang J, Qian J, Wezeman M, Kwak LW, Yi Q. Tumor evasion of the immune system: inhibiting p38 MAPK signaling restores the function of dendritic cells in multiple myeloma. *Blood*. 2006; 107:2432-2439.
548. Mori Y, Shimizu N, Dallas M, *et al*. Anti-alpha4 integrin antibody suppresses the development of multiple myeloma and associated osteoclastic osteolysis. *Blood*. 2004; 104:2149-2154.
549. Oyajobi BO, Franchin G, Williams PJ, *et al*. Dual effects of macrophage inflammatory protein-1alpha on osteolysis and tumor burden in the murine 5TGM1 model of myeloma bone disease. *Blood*. 2003; 102:311-319.
550. Oyajobi BO, Mundy GR. Receptor activator of NF-kappaB ligand, macrophage inflammatory protein-1alpha, and the proteasome: novel therapeutic targets in myeloma. *Cancer*. 2003; 97:813-817.
551. Miao Z, Luker KE, Summers BC, *et al*. CXCR7 (RDC1) promotes breast and lung tumor growth in vivo and is expressed on tumor-associated vasculature. *Proc Natl Acad Sci U S A*. 2007; 104:15735-15740.
552. Jurczyszyn A, Wolska-Smolen T, Skotnicki AB. [Multiple myeloma: the role of angiogenesis and therapeutic application of thalidomide]. *Przegl Lek*. 2003; 60:542-547.
553. Shin DH, Chun YS, Lee DS, Huang LE, Park JW. Bortezomib inhibits tumor adaptation to hypoxia by stimulating the FIH-mediated repression of hypoxia-inducible factor-1. *Blood*. 2008; 111:3131-3136.
554. Richardson PG, Schlossman RL, Weller E, *et al*. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood*. 2002; 100:3063-3067.

## **APPENDICES**



**Appendix 1. The CXCL12 Promoter Sequence.** The two consensus HIF binding sites, designated HBS1 and HBS2, are highlighted in red. The PCR primers used to amplify HBS1 and HBS2 for ChIP analyses are coloured green and purple, respectively. The PCR primers used to clone the full CXCL12 promoter into the pGL3b luciferase vector are coloured orange.