

Tesi doctoral presentada per En/Na

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amb el títol

**" Identificació, aïllament i caracterització de cèl.lules
mare en models de càncer de pròstata "**

per a l'obtenció del títol de Doctor/a en

MEDICINA

Barcelona, 11 de juny de 2009.

**Facultat de Medicina
Departament de Biologia Cel.lular, Immunologia
i Neurociències**



UNIVERSITAT DE BARCELONA





El filtre de la paraula humana obra tan poderosament en el sentit dels homes que, quan s'estronca, aquests s'en senten angoixosament anyoradiços.

Víctor Català, Solitut (edició de 1929)

La science n'a pas de patrie, mais le savant, en a une.

Louis Pasteur



7. REFERÈNCIES

Reproducció parcial de la il·lustració de la portada de la primera edició de Solitut (1904-1905), de Caterina Albert i Paradís.

1. Petersen, R. *Prostate*, (JB Lippincott, Philadelphia, 1986).
2. WM Murphey, J.G. *Diseases of the prostate gland and seminal vesicles*, (WB Saunders, Philadelphia, 1989).
3. Gleason, D. *The Veteran's Administration Cooperative Urologic Research Group: histologic grading and clinical staging of prostatic carcinoma*, (Lea and Febiger, Philadelphia, 1977).
4. Stanbrough, M., *et al.* Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. *Cancer research* 66, 2815-2825 (2006).
5. Mostaghel, E.A., *et al.* Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. *Cancer research* 67, 5033-5041 (2007).
6. Ruijter, E., *et al.* Molecular genetics and epidemiology of prostate carcinoma. *Endocrine reviews* 20, 22-45 (1999).
7. Chen, C.D., *et al.* Molecular determinants of resistance to antiandrogen therapy. *Nature medicine* 10, 33-39 (2004).
8. Lee, W.H., *et al.* Cytidine methylation of regulatory sequences near the pi-class glutathione S-transferase gene accompanies human prostatic carcinogenesis. *Proceedings of the National Academy of Sciences of the United States of America* 91, 11733-11737 (1994).
9. Hyytinen, E.R., *et al.* Genetic changes associated with the acquisition of androgen-independent growth, tumorigenicity and metastatic potential in a prostate cancer model. *British journal of cancer* 75, 190-195 (1997).
10. Pilat, M.J., Kamradt, J.M. & Pienta, K.J. Hormone resistance in prostate cancer. *Cancer metastasis reviews* 17, 373-381 (1998).
11. Pulukuri, S.M., Estes, N., Patel, J. & Rao, J.S. Demethylation-linked activation of urokinase plasminogen activator is involved in progression of prostate cancer. *Cancer research* 67, 930-939 (2007).
12. Pulukuri, S.M. & Rao, J.S. Small interfering RNA directed reversal of urokinase plasminogen activator demethylation inhibits prostate tumor growth and metastasis. *Cancer research* 67, 6637-6646 (2007).
13. Verkaik, N.S., van Steenbrugge, G.J., van Weerden, W.M., Bussemakers, M.J. & van der Kwast, T.H. Silencing of CD44 expression in prostate cancer by hypermethylation of the CD44 promoter region. *Laboratory investigation; a journal of technical methods and pathology* 80, 1291-1298 (2000).
14. Pulukuri, S.M., Patibandla, S., Patel, J., Estes, N. & Rao, J.S. Epigenetic inactivation of the tissue inhibitor of metalloproteinase-2 (TIMP-2) gene in human prostate tumors. *Oncogene* 26, 5229-5237 (2007).
15. Shiina, H., *et al.* Functional Loss of the gamma-catenin gene through epigenetic and genetic pathways in human prostate cancer. *Cancer research* 65, 2130-2138 (2005).
16. Murillo, H., *et al.* Prostate cancer cells use genetic and epigenetic mechanisms for progression to androgen independence. *Genes, chromosomes & cancer* 45, 702-716 (2006).

17. Turley, R.S., *et al.* The type III transforming growth factor-beta receptor as a novel tumor suppressor gene in prostate cancer. *Cancer research* 67, 1090-1098 (2007).
18. Marcelli, M., *et al.* Androgen receptor mutations in prostate cancer. *Cancer research* 60, 944-949 (2000).
19. Taplin, M.E., *et al.* Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *The New England journal of medicine* 332, 1393-1398 (1995).
20. Culig, Z., *et al.* Expression, structure, and function of androgen receptor in advanced prostatic carcinoma. *Prostate* 35, 63-70 (1998).
21. Craft, N., *et al.* Evidence for clonal outgrowth of androgen-independent prostate cancer cells from androgen-dependent tumors through a two-step process. *Cancer research* 59, 5030-5036 (1999).
22. Taplin, M.E., *et al.* Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. *Cancer research* 59, 2511-2515 (1999).
23. Bruchofsky, N., *et al.* Intermittent androgen suppression for prostate cancer: Canadian Prospective Trial and related observations. *Molecular urology* 4, 191-199;discussion 201 (2000).
24. Conti, P.D., *et al.* Intermittent versus continuous androgen suppression for prostatic cancer. *Cochrane database of systematic reviews (Online)*, CD005009 (2007).
25. Rocco, B., Scardino, E. & de Cobelli, O. Locally advanced prostate cancer: biochemical results from a prospective phase II study of intermittent androgen suppression for men with evidence of prostate-specific antigen recurrence after radiotherapy. *Cancer* 110, 467-468; author reply 468 (2007).
26. Bruchofsky, N., *et al.* Quality of life, morbidity, and mortality results of a prospective phase II study of intermittent androgen suppression for men with evidence of prostate-specific antigen relapse after radiation therapy for locally advanced prostate cancer. *Clinical genitourinary cancer* 6, 46-52 (2008).
27. Feldman, B.J. & Feldman, D. The development of androgen-independent prostate cancer. *Nature reviews* 1, 34-45 (2001).
28. Isaacs, J.T. The biology of hormone refractory prostate cancer. Why does it develop? *The Urologic clinics of North America* 26, 263-273 (1999).
29. Isaacs, J.T. & Coffey, D.S. Adaptation versus selection as the mechanism responsible for the relapse of prostatic cancer to androgen ablation therapy as studied in the Dunning R-3327-H adenocarcinoma. *Cancer research* 41, 5070-5075 (1981).
30. Cunha, G.R., Hayward, S.W. & Wang, Y.Z. Role of stroma in carcinogenesis of the prostate. *Differentiation; research in biological diversity* 70, 473-485 (2002).
31. Hayward, S.W., *et al.* Malignant transformation in a nontumorigenic human prostatic epithelial cell line. *Cancer research* 61, 8135-8142 (2001).
32. Cunha, G.R. & Donjacour, A. Stromal-epithelial interactions in normal and abnormal prostatic development. *Progress in clinical and biological research* 239, 251-272 (1987).
33. Giri, D., Ropiquet, F. & Ittmann, M. Alterations in expression of basic fibroblast growth factor (FGF) 2 and its receptor FGFR-1 in human prostate cancer. *Clin Cancer Res* 5, 1063-1071 (1999).

34. Yan, G., Fukabori, Y., McBride, G., Nikolaropolous, S. & McKeehan, W.L. Exon switching and activation of stromal and embryonic fibroblast growth factor (FGF)-FGF receptor genes in prostate epithelial cells accompany stromal independence and malignancy. *Molecular and cellular biology* 13, 4513-4522 (1993).
35. Lu, W., Luo, Y., Kan, M. & McKeehan, W.L. Fibroblast growth factor-10. A second candidate stromal to epithelial cell andromedin in prostate. *The Journal of biological chemistry* 274, 12827-12834 (1999).
36. Nakano, K., *et al.* Androgen-stimulated human prostate epithelial growth mediated by stromal-derived fibroblast growth factor-10. *Endocrine journal* 46, 405-413 (1999).
37. Wu, X., Jin, C., Wang, F., Yu, C. & McKeehan, W.L. Stromal cell heterogeneity in fibroblast growth factor-mediated stromal-epithelial cell cross-talk in premalignant prostate tumors. *Cancer research* 63, 4936-4944 (2003).
38. Jin, C., *et al.* Directionally specific paracrine communication mediated by epithelial FGF9 to stromal FGFR3 in two-compartment premalignant prostate tumors. *Cancer research* 64, 4555-4562 (2004).
39. Acevedo, V.D., *et al.* Inducible FGFR-1 activation leads to irreversible prostate adenocarcinoma and an epithelial-to-mesenchymal transition. *Cancer cell* 12, 559-571 (2007).
40. Memarzadeh, S., *et al.* Enhanced paracrine FGF10 expression promotes formation of multifocal prostate adenocarcinoma and an increase in epithelial androgen receptor. *Cancer cell* 12, 572-585 (2007).
41. Winter, S.F., *et al.* Conditional activation of FGFR1 in the prostate epithelium induces angiogenesis with concomitant differential regulation of Ang-1 and Ang-2. *Oncogene* 26, 4897-4907 (2007).
42. Yang, F., Strand, D.W. & Rowley, D.R. Fibroblast growth factor-2 mediates transforming growth factor-beta action in prostate cancer reactive stroma. *Oncogene* 27, 450-459 (2008).
43. Tu, W.H., *et al.* The loss of TGF-beta signaling promotes prostate cancer metastasis. *Neoplasia (New York, N.Y)* 5, 267-277 (2003).
44. Bhowmick, N.A., *et al.* TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. *Science (New York, N.Y)* 303, 848-851 (2004).
45. Olumi, A.F., *et al.* Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. *Cancer research* 59, 5002-5011 (1999).
46. Tuxhorn, J.A., McAlhany, S.J., Dang, T.D., Ayala, G.E. & Rowley, D.R. Stromal cells promote angiogenesis and growth of human prostate tumors in a differential reactive stroma (DRS) xenograft model. *Cancer research* 62, 3298-3307 (2002).
47. Ohlson, N., Bergh, A., Stattin, P. & Wikstrom, P. Castration-induced epithelial cell death in human prostate tissue is related to locally reduced IGF-1 levels. *Prostate* 67, 32-40 (2007).
48. Halin, S., Hammarsten, P., Wikstrom, P. & Bergh, A. Androgen-insensitive prostate cancer cells transiently respond to castration treatment when growing in an androgen-dependent prostate environment. *Prostate* 67, 370-377 (2007).

49. de Pinieux, G., *et al.* Clinical and experimental progression of a new model of human prostate cancer and therapeutic approach. *The American journal of pathology* 159, 753-764 (2001).
50. Fan, L., *et al.* Hedgehog signaling promotes prostate xenograft tumor growth. *Endocrinology* 145, 3961-3970 (2004).
51. Okamoto, R., *et al.* Hematopoietic cells regulate the angiogenic switch during tumorigenesis. *Blood* 105, 2757-2763 (2005).
52. Li, H., Gerald, W.L. & Benezra, R. Utilization of bone marrow-derived endothelial cell precursors in spontaneous prostate tumors varies with tumor grade. *Cancer research* 64, 6137-6143 (2004).
53. Barrett, J.M., Mangold, K.A., Jilling, T. & Kaul, K.L. Bi-directional interactions of prostate cancer cells and bone marrow endothelial cells in three-dimensional culture. *Prostate* 64, 75-82 (2005).
54. Barrett, J.M., *et al.* Prostate cancer cells regulate growth and differentiation of bone marrow endothelial cells through TGFbeta and its receptor, TGFbetaRII. *Prostate* 66, 632-650 (2006).
55. Coussens, L.M., Tinkle, C.L., Hanahan, D. & Werb, Z. MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. *Cell* 103, 481-490 (2000).
56. Kaplan, R.N., *et al.* VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature* 438, 820-827 (2005).
57. Glinsky, G.V., Berezovska, O. & Glinskii, A.B. Microarray analysis identifies a death-from-cancer signature predicting therapy failure in patients with multiple types of cancer. *The Journal of clinical investigation* 115, 1503-1521 (2005).
58. Weigelt, B., Peterse, J.L. & van 't Veer, L.J. Breast cancer metastasis: markers and models. *Nature reviews* 5, 591-602 (2005).
59. Bernards, R. & Weinberg, R.A. A progression puzzle. *Nature* 418, 823 (2002).
60. Fidler, I.J. Tumor heterogeneity and the biology of cancer invasion and metastasis. *Cancer research* 38, 2651-2660 (1978).
61. Fidler, I.J. & Hart, I.R. Biological diversity in metastatic neoplasms: origins and implications. *Science (New York, N.Y)* 217, 998-1003 (1982).
62. Talmadge, J.E., Wolman, S.R. & Fidler, I.J. Evidence for the clonal origin of spontaneous metastases. *Science (New York, N.Y)* 217, 361-363 (1982).
63. Ramaswamy, S., Ross, K.N., Lander, E.S. & Golub, T.R. A molecular signature of metastasis in primary solid tumors. *Nature genetics* 33, 49-54 (2003).
64. Southam C.M., B.A. Quantitative studies of autotransplantation of human cancer. *Cancer* 14(1961).
65. Salsbury, A.J. The significance of the circulating cancer cell. *Cancer treatment reviews* 2, 55-72 (1975).
66. Hamburger, A.W. & Salmon, S.E. Primary bioassay of human tumor stem cells. *Science (New York, N.Y)* 197, 461-463 (1977).

67. Wheelock, E.F., Weinhold, K.J. & Levich, J. The tumor dormant state. *Advances in cancer research* 34, 107-140 (1981).
68. Gimbrone, M.A., Jr., Leapman, S.B., Cotran, R.S. & Folkman, J. Tumor dormancy in vivo by prevention of neovascularization. *The Journal of experimental medicine* 136, 261-276 (1972).
69. Holmgren, L., O'Reilly, M.S. & Folkman, J. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. *Nature medicine* 1, 149-153 (1995).
70. Udagawa, T., Fernandez, A., Achilles, E.G., Folkman, J. & D'Amato, R.J. Persistence of microscopic human cancers in mice: alterations in the angiogenic balance accompanies loss of tumor dormancy. *Faseb J* 16, 1361-1370 (2002).
71. Almog, N., *et al.* Prolonged dormancy of human liposarcoma is associated with impaired tumor angiogenesis. *Faseb J* 20, 947-949 (2006).
72. Naumov, G.N., *et al.* A model of human tumor dormancy: an angiogenic switch from the nonangiogenic phenotype. *Journal of the National Cancer Institute* 98, 316-325 (2006).
73. Udagawa, T., Puder, M., Wood, M., Schaefer, B.C. & D'Amato, R.J. Analysis of tumor-associated stromal cells using SCID GFP transgenic mice: contribution of local and bone marrow-derived host cells. *Faseb J* 20, 95-102 (2006).
74. Zippelius, A., *et al.* Limitations of reverse-transcriptase polymerase chain reaction analyses for detection of micrometastatic epithelial cancer cells in bone marrow. *J Clin Oncol* 15, 2701-2708 (1997).
75. Dimmler, A., *et al.* Transcription of cytokeratins 8, 18, and 19 in bone marrow and limited expression of cytokeratins 7 and 20 by carcinoma cells: inherent limitations for RT-PCR in the detection of isolated tumor cells. *Laboratory investigation; a journal of technical methods and pathology* 81, 1351-1361 (2001).
76. Ahr, A., *et al.* Cross-reactive staining of normal bone-marrow cells by monoclonal antibody 2E11. *International journal of cancer* 84, 502-505 (1999).
77. Pantel, K., *et al.* Methodological analysis of immunocytochemical screening for disseminated epithelial tumor cells in bone marrow. *Journal of hematotherapy* 3, 165-173 (1994).
78. Braun, S. & Pantel, K. Biological characteristics of micrometastatic cancer cells in bone marrow. *Cancer metastasis reviews* 18, 75-90 (1999).
79. Putz, E., *et al.* Phenotypic characteristics of cell lines derived from disseminated cancer cells in bone marrow of patients with solid epithelial tumors: establishment of working models for human micrometastases. *Cancer research* 59, 241-248 (1999).
80. Braun, S., *et al.* Lack of effect of adjuvant chemotherapy on the elimination of single dormant tumor cells in bone marrow of high-risk breast cancer patients. *J Clin Oncol* 18, 80-86 (2000).
81. Melchior, S.W., *et al.* Early tumor cell dissemination in patients with clinically localized carcinoma of the prostate. *Clin Cancer Res* 3, 249-256 (1997).
82. Braun, S., *et al.* A pooled analysis of bone marrow micrometastasis in breast cancer. *The New England journal of medicine* 353, 793-802 (2005).

83. Pantel, K., *et al.* Immunocytochemical detection of isolated tumour cells in bone marrow of patients with untreated stage C prostatic cancer. *Eur J Cancer* 31A, 1627-1632 (1995).
84. Braun, S., *et al.* Cytokeratin-positive cells in the bone marrow and survival of patients with stage I, II, or III breast cancer. *The New England journal of medicine* 342, 525-533 (2000).
85. Lilleby, W., *et al.* The prognostic impact of cytokeratin-positive cells in bone marrow of patients with localized prostate cancer. *International journal of cancer* 103, 91-96 (2003).
86. Woelfle, U., *et al.* Molecular signature associated with bone marrow micrometastasis in human breast cancer. *Cancer research* 63, 5679-5684 (2003).
87. Horoszewicz, J.S., *et al.* The LNCaP cell line--a new model for studies on human prostatic carcinoma. *Progress in clinical and biological research* 37, 115-132 (1980).
88. Kaighn, M.E., *et al.* The Pasadena cell lines. *Progress in clinical and biological research* 37, 85-109 (1980).
89. Mickey, D.D., Stone, K.R., Wunderli, H., Mickey, G.H. & Paulson, D.F. Characterization of a human prostate adenocarcinoma cell line (DU 145) as a monolayer culture and as a solid tumor in athymic mice. *Progress in clinical and biological research* 37, 67-84 (1980).
90. Greenberg, N.M., *et al.* Prostate cancer in a transgenic mouse. *Proceedings of the National Academy of Sciences of the United States of America* 92, 3439-3443 (1995).
91. Wang, S., *et al.* Prostate-specific deletion of the murine Pten tumor suppressor gene leads to metastatic prostate cancer. *Cancer cell* 4, 209-221 (2003).
92. Wainstein, M.A., *et al.* CWR22: androgen-dependent xenograft model derived from a primary human prostatic carcinoma. *Cancer research* 54, 6049-6052 (1994).
93. Royai, R., Lange, P.H. & Vessella, R. Preclinical models of prostate cancer. *Seminars in oncology* 23, 35-40 (1996).
94. Stearns, M.E., *et al.* Workgroup 2: human xenograft models of prostate cancer. *Prostate* 36, 56-58 (1998).
95. Dunning, W.F. Prostate Cancer in the Rat. *National Cancer Institute monograph* 12, 351-369 (1963).
96. Noble, R.L. Hormonal control of growth and progression in tumors of Nb rats and a theory of action. *Cancer research* 37, 82-94 (1977).
97. Pollard, M. Spontaneous prostate adenocarcinomas in aged germfree Wistar rats. *Journal of the National Cancer Institute* 51, 1235-1241 (1973).
98. Isaacs, J.T. The aging ACI/Seg versus Copenhagen male rat as a model system for the study of prostatic carcinogenesis. *Cancer research* 44, 5785-5796 (1984).
99. Spangrude, G.J., Heimfeld, S. & Weissman, I.L. Purification and characterization of mouse hematopoietic stem cells. *Science (New York, N.Y)* 241, 58-62 (1988).
100. Baum, C.M., Weissman, I.L., Tsukamoto, A.S., Buckle, A.M. & Peault, B. Isolation of a candidate human hematopoietic stem-cell population. *Proceedings of the National Academy of Sciences of the United States of America* 89, 2804-2808 (1992).

101. Morrison, S.J. & Weissman, I.L. The long-term repopulating subset of hematopoietic stem cells is deterministic and isolatable by phenotype. *Immunity* 1, 661-673 (1994).
102. Osawa, M., Hanada, K., Hamada, H. & Nakauchi, H. Long-term lymphohematopoietic reconstitution by a single CD34-low/negative hematopoietic stem cell. *Science (New York, N.Y)* 273, 242-245 (1996).
103. Petersen, B.E., *et al.* Bone marrow as a potential source of hepatic oval cells. *Science (New York, N.Y)* 284, 1168-1170 (1999).
104. Lagasse, E., *et al.* Purified hematopoietic stem cells can differentiate into hepatocytes in vivo. *Nature medicine* 6, 1229-1234 (2000).
105. Mezey, E., Chandross, K.J., Harta, G., Maki, R.A. & McKercher, S.R. Turning blood into brain: cells bearing neuronal antigens generated in vivo from bone marrow. *Science (New York, N.Y)* 290, 1779-1782 (2000).
106. Krause, D.S., *et al.* Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. *Cell* 105, 369-377 (2001).
107. Friedenstein, A.J., Petrakova, K.V., Kurolesova, A.I. & Frolova, G.P. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. *Transplantation* 6, 230-247 (1968).
108. Friedenstein, A.J., Chailakhjan, R.K. & Lalykina, K.S. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. *Cell and tissue kinetics* 3, 393-403 (1970).
109. Friedenstein, A.J., Chailakhyan, R.K., Latsinik, N.V., Panasyuk, A.F. & Keiliss-Borok, I.V. Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues. Cloning in vitro and retransplantation in vivo. *Transplantation* 17, 331-340 (1974).
110. Friedenstein, A.J., *et al.* Precursors for fibroblasts in different populations of hematopoietic cells as detected by the in vitro colony assay method. *Experimental hematology* 2, 83-92 (1974).
111. Friedenstein, A.J., Gorskaja, J.F. & Kulagina, N.N. Fibroblast precursors in normal and irradiated mouse hematopoietic organs. *Experimental hematology* 4, 267-274 (1976).
112. Friedenstein, A.J. Stromal mechanisms of bone marrow: cloning in vitro and retransplantation in vivo. *Haematology and blood transfusion* 25, 19-29 (1980).
113. Friedenstein, A.J., Chailakhyan, R.K. & Gerasimov, U.V. Bone marrow osteogenic stem cells: in vitro cultivation and transplantation in diffusion chambers. *Cell and tissue kinetics* 20, 263-272 (1987).
114. Liechty, K.W., *et al.* Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after in utero transplantation in sheep. *Nature medicine* 6, 1282-1286 (2000).
115. Dominici, M., *et al.* Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 8, 315-317 (2006).
116. Baddoo, M., *et al.* Characterization of mesenchymal stem cells isolated from murine bone marrow by negative selection. *Journal of cellular biochemistry* 89, 1235-1249 (2003).

117. Romanov, Y.A., Svintsitskaya, V.A. & Smirnov, V.N. Searching for alternative sources of postnatal human mesenchymal stem cells: candidate MSC-like cells from umbilical cord. *Stem cells (Dayton, Ohio)* 21, 105-110 (2003).
118. Bieback, K., Kern, S., Kluter, H. & Eichler, H. Critical parameters for the isolation of mesenchymal stem cells from umbilical cord blood. *Stem cells (Dayton, Ohio)* 22, 625-634 (2004).
119. Igura, K., *et al.* Isolation and characterization of mesenchymal progenitor cells from chorionic villi of human placenta. *Cytotherapy* 6, 543-553 (2004).
120. Tsai, M.S., Lee, J.L., Chang, Y.J. & Hwang, S.M. Isolation of human multipotent mesenchymal stem cells from second-trimester amniotic fluid using a novel two-stage culture protocol. *Human reproduction (Oxford, England)* 19, 1450-1456 (2004).
121. Warejcka, D.J., Harvey, R., Taylor, B.J., Young, H.E. & Lucas, P.A. A population of cells isolated from rat heart capable of differentiating into several mesodermal phenotypes. *The Journal of surgical research* 62, 233-242 (1996).
122. Young, H.E., *et al.* Mesenchymal stem cells reside within the connective tissues of many organs. *Dev Dyn* 202, 137-144 (1995).
123. Katz, A.J., Tholpady, A., Tholpady, S.S., Shang, H. & Ogle, R.C. Cell surface and transcriptional characterization of human adipose-derived adherent stromal (hADAS) cells. *Stem cells (Dayton, Ohio)* 23, 412-423 (2005).
124. Fickert, S., Fiedler, J. & Brenner, R.E. Identification, quantification and isolation of mesenchymal progenitor cells from osteoarthritic synovium by fluorescence automated cell sorting. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 11, 790-800 (2003).
125. Hu, Y., *et al.* Isolation and identification of mesenchymal stem cells from human fetal pancreas. *The Journal of laboratory and clinical medicine* 141, 342-349 (2003).
126. Luria, E.A., Panasyuk, A.F. & Friedenstein, A.Y. Fibroblast colony formation from monolayer cultures of blood cells. *Transfusion* 11, 345-349 (1971).
127. Kuznetsov, S.A., *et al.* Circulating skeletal stem cells. *The Journal of cell biology* 153, 1133-1140 (2001).
128. Baksh, D., Song, L. & Tuan, R.S. Adult mesenchymal stem cells: characterization, differentiation, and application in cell and gene therapy. *Journal of cellular and molecular medicine* 8, 301-316 (2004).
129. Sotiropoulou, P.A., Perez, S.A., Salagianni, M., Baxevanis, C.N. & Papamichail, M. Characterization of the optimal culture conditions for clinical scale production of human mesenchymal stem cells. *Stem cells (Dayton, Ohio)* 24, 462-471 (2006).
130. Le Blanc, K., *et al.* Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. *Lancet* 363, 1439-1441 (2004).
131. Aggarwal, S. & Pittenger, M.F. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood* 105, 1815-1822 (2005).
132. Chamberlain, J.R., *et al.* Gene targeting in stem cells from individuals with osteogenesis imperfecta. *Science (New York, N.Y)* 303, 1198-1201 (2004).

133. Le Blanc, K., *et al.* Fetal mesenchymal stem-cell engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. *Transplantation* 79, 1607-1614 (2005).
134. Isaacs, J.T. & Coffey, D.S. Etiology and disease process of benign prostatic hyperplasia. *The Prostate* 2, 33-50 (1989).
135. English, H.F., Santen, R.J. & Isaacs, J.T. Response of glandular versus basal rat ventral prostatic epithelial cells to androgen withdrawal and replacement. *Prostate* 11, 229-242 (1987).
136. Isaacs, J.T. Control of cell proliferation and cell death in the normal and neoplastic prostate: a stem cell model. in *Benign prostatic hyperplasia* (ed. Rodgers, C.) (Department of Health and Human Services, Washington, DC, 1985).
137. Mills, A.A., *et al.* p63 is a p53 homologue required for limb and epidermal morphogenesis. *Nature* 398, 708-713 (1999).
138. Yang, A., *et al.* p63 is essential for regenerative proliferation in limb, craniofacial and epithelial development. *Nature* 398, 714-718 (1999).
139. Signoretti, S., *et al.* p63 is a prostate basal cell marker and is required for prostate development. *The American journal of pathology* 157, 1769-1775 (2000).
140. Mills, A.A., Qi, Y. & Bradley, A. Conditional inactivation of p63 by Cre-mediated excision. *Genesis* 32, 138-141 (2002).
141. Signoretti, S., *et al.* p63 regulates commitment to the prostate cell lineage. *Proceedings of the National Academy of Sciences of the United States of America* 102, 11355-11360 (2005).
142. Hudson, D.L., O'Hare, M., Watt, F.M. & Masters, J.R. Proliferative heterogeneity in the human prostate: evidence for epithelial stem cells. *Laboratory investigation; a journal of technical methods and pathology* 80, 1243-1250 (2000).
143. Verhagen, A.P., Aalders, T.W., Ramaekers, F.C., Debruyne, F.M. & Schalken, J.A. Differential expression of keratins in the basal and luminal compartments of rat prostatic epithelium during degeneration and regeneration. *Prostate* 13, 25-38 (1988).
144. van Leenders, G.J. & Schalken, J.A. Stem cell differentiation within the human prostate epithelium: implications for prostate carcinogenesis. *BJU international* 88 Suppl 2, 35-42; discussion 49-50 (2001).
145. Xue, Y., Smedts, F., Debruyne, F.M., de la Rosette, J.J. & Schalken, J.A. Identification of intermediate cell types by keratin expression in the developing human prostate. *Prostate* 34, 292-301 (1998).
146. van Leenders, G., Dijkman, H., Hulsbergen-van de Kaa, C., Ruiter, D. & Schalken, J. Demonstration of intermediate cells during human prostate epithelial differentiation in situ and in vitro using triple-staining confocal scanning microscopy. *Laboratory investigation; a journal of technical methods and pathology* 80, 1251-1258 (2000).
147. Wang, Y., Hayward, S., Cao, M., Thayer, K. & Cunha, G. Cell differentiation lineage in the prostate. *Differentiation; research in biological diversity* 68, 270-279 (2001).
148. Liu, A.Y., *et al.* Cell-cell interaction in prostate gene regulation and cytodifferentiation. *Proceedings of the National Academy of Sciences of the United States of America* 94, 10705-10710 (1997).

149. Robinson, E.J., Neal, D.E. & Collins, A.T. Basal cells are progenitors of luminal cells in primary cultures of differentiating human prostatic epithelium. *Prostate* 37, 149-160 (1998).
150. Tran, C.P., Lin, C., Yamashiro, J. & Reiter, R.E. Prostate stem cell antigen is a marker of late intermediate prostate epithelial cells. *Mol Cancer Res* 1, 113-121 (2002).
151. Verhagen, A.P., *et al.* Colocalization of basal and luminal cell-type cytokeratins in human prostate cancer. *Cancer research* 52, 6182-6187 (1992).
152. Richardson, G.D., *et al.* CD133, a novel marker for human prostatic epithelial stem cells. *Journal of cell science* 117, 3539-3545 (2004).
153. Tsujimura, A., *et al.* Proximal location of mouse prostate epithelial stem cells: a model of prostatic homeostasis. *The Journal of cell biology* 157, 1257-1265 (2002).
154. Salm, S.N., *et al.* TGF- β maintains dormancy of prostatic stem cells in the proximal region of ducts. *The Journal of cell biology* 170, 81-90 (2005).
155. Goto, K., *et al.* Proximal prostatic stem cells are programmed to regenerate a proximal-distal ductal axis. *Stem cells (Dayton, Ohio)* 24, 1859-1868 (2006).
156. Meeker, A.K., Sommerfeld, H.J. & Coffey, D.S. Telomerase is activated in the prostate and seminal vesicles of the castrated rat. *Endocrinology* 137, 5743-5746 (1996).
157. Bhatt, R.I., *et al.* Novel method for the isolation and characterisation of the putative prostatic stem cell. *Cytometry A* 54, 89-99 (2003).
158. Goodell, M.A., Brose, K., Paradis, G., Conner, A.S. & Mulligan, R.C. Isolation and functional properties of murine hematopoietic stem cells that are replicating in vivo. *The Journal of experimental medicine* 183, 1797-1806 (1996).
159. Ingham, P.W. & McMahon, A.P. Hedgehog signaling in animal development: paradigms and principles. *Genes & development* 15, 3059-3087 (2001).
160. Karhadkar, S.S., *et al.* Hedgehog signalling in prostate regeneration, neoplasia and metastasis. *Nature* 431, 707-712 (2004).
161. Sanchez, P., *et al.* Inhibition of prostate cancer proliferation by interference with SONIC HEDGEHOG-GLI1 signaling. *Proceedings of the National Academy of Sciences of the United States of America* 101, 12561-12566 (2004).
162. Reya, T., Morrison, S.J., Clarke, M.F. & Weissman, I.L. Stem cells, cancer, and cancer stem cells. *Nature* 414, 105-111 (2001).
163. Sawyers, C.L., Denny, C.T. & Witte, O.N. Leukemia and the disruption of normal hematopoiesis. *Cell* 64, 337-350 (1991).
164. Sell, S. & Pierce, G.B. Maturation arrest of stem cell differentiation is a common pathway for the cellular origin of teratocarcinomas and epithelial cancers. *Laboratory investigation; a journal of technical methods and pathology* 70, 6-22 (1994).
165. Fialkow, P.J. Clonal origin of human tumors. *Biochimica et biophysica acta* 458, 283-321 (1976).
166. Fearon, E.R., Hamilton, S.R. & Vogelstein, B. Clonal analysis of human colorectal tumors. *Science (New York, N.Y)* 238, 193-197 (1987).

167. Dean, M., Fojo, T. & Bates, S. Tumour stem cells and drug resistance. *Nature reviews* 5, 275-284 (2005).
168. O'Brien, C.A., Pollett, A., Gallinger, S. & Dick, J.E. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. *Nature* 445, 106-110 (2007).
169. Al-Hajj, M., Wicha, M.S., Benito-Hernandez, A., Morrison, S.J. & Clarke, M.F. Prospective identification of tumorigenic breast cancer cells. *Proceedings of the National Academy of Sciences of the United States of America* 100, 3983-3988 (2003).
170. Bonnet, D. & Dick, J.E. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nature medicine* 3, 730-737 (1997).
171. Litvinov, I.V., De Marzo, A.M. & Isaacs, J.T. Is the Achilles' heel for prostate cancer therapy a gain of function in androgen receptor signaling? *The Journal of clinical endocrinology and metabolism* 88, 2972-2982 (2003).
172. Collins, A.T., Berry, P.A., Hyde, C., Stower, M.J. & Maitland, N.J. Prospective identification of tumorigenic prostate cancer stem cells. *Cancer research* 65, 10946-10951 (2005).
173. Sharifi, N., Hurt, E.M. & Farrar, W.L. Androgen receptor expression in prostate cancer stem cells: is there a conundrum? *Cancer chemotherapy and pharmacology* 62, 921-923 (2008).
174. Patrawala, L., *et al.* Highly purified CD44+ prostate cancer cells from xenograft human tumors are enriched in tumorigenic and metastatic progenitor cells. *Oncogene* 25, 1696-1708 (2006).
175. Patrawala, L., Calhoun-Davis, T., Schneider-Broussard, R. & Tang, D.G. Hierarchical organization of prostate cancer cells in xenograft tumors: the CD44+alpha2beta1+ cell population is enriched in tumor-initiating cells. *Cancer research* 67, 6796-6805 (2007).
176. Patrawala, L., *et al.* Side population is enriched in tumorigenic, stem-like cancer cells, whereas ABCG2+ and ABCG2- cancer cells are similarly tumorigenic. *Cancer research* 65, 6207-6219 (2005).
177. Wang, S., *et al.* Pten deletion leads to the expansion of a prostatic stem/progenitor cell subpopulation and tumor initiation. *Proceedings of the National Academy of Sciences of the United States of America* 103, 1480-1485 (2006).
178. Zhou, Z., Flesken-Nikitin, A. & Nikitin, A.Y. Prostate cancer associated with p53 and Rb deficiency arises from the stem/progenitor cell-enriched proximal region of prostatic ducts. *Cancer research* 67, 5683-5690 (2007).
179. Burger, P.E., *et al.* Sca-1 expression identifies stem cells in the proximal region of prostatic ducts with high capacity to reconstitute prostatic tissue. *Proceedings of the National Academy of Sciences of the United States of America* 102, 7180-7185 (2005).
180. Zhou, S., *et al.* The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. *Nature medicine* 7, 1028-1034 (2001).
181. Chaudhary, P.M. & Roninson, I.B. Expression and activity of P-glycoprotein, a multidrug efflux pump, in human hematopoietic stem cells. *Cell* 66, 85-94 (1991).
182. Bunting, K.D., Galipeau, J., Topham, D., Benaim, E. & Sorrentino, B.P. Transduction of murine bone marrow cells with an MDR1 vector enables ex vivo stem cell expansion, but

- these expanded grafts cause a myeloproliferative syndrome in transplanted mice. *Blood* 92, 2269-2279 (1998).
183. Bunting, K.D., Zhou, S., Lu, T. & Sorrentino, B.P. Enforced P-glycoprotein pump function in murine bone marrow cells results in expansion of side population stem cells in vitro and repopulating cells in vivo. *Blood* 96, 902-909 (2000).
 184. Scharenberg, C.W., Harkey, M.A. & Torok-Storb, B. The ABCG2 transporter is an efficient Hoechst 33342 efflux pump and is preferentially expressed by immature human hematopoietic progenitors. *Blood* 99, 507-512 (2002).
 185. Pearce, D.J., Ridler, C.M., Simpson, C. & Bonnet, D. Multiparameter analysis of murine bone marrow side population cells. *Blood* 103, 2541-2546 (2004).
 186. Nadin, B.M., Goodell, M.A. & Hirschi, K.K. Phenotype and hematopoietic potential of side
 187. Montanaro, F., *et al.* Demystifying SP cell purification: viability, yield, and phenotype are defined by isolation parameters. *Experimental cell research* 298, 144-154 (2004).
 188. Uchida, N., *et al.* ABC transporter activities of murine hematopoietic stem cells vary according to their developmental and activation status. *Blood* 103, 4487-4495 (2004).
 189. Sales-Pardo, I., *et al.* Flow cytometry of the Side Population: tips & tricks. *Cell Oncol* 28, 37-53 (2006).
 190. Gros, P., Croop, J. & Housman, D. Mammalian multidrug resistance gene: complete cDNA sequence indicates strong homology to bacterial transport proteins. *Cell* 47, 371-380 (1986).
 191. Doyle, L.A., *et al.* A multidrug resistance transporter from human MCF-7 breast cancer cells. *Proceedings of the National Academy of Sciences of the United States of America* 95, 15665-15670 (1998).
 192. Allen, J.D., Brinkhuis, R.F., Wijnholds, J. & Schinkel, A.H. The mouse Bcrp1/Mxr/Abcp gene: amplification and overexpression in cell lines selected for resistance to topotecan, mitoxantrone, or doxorubicin. *Cancer research* 59, 4237-4241 (1999).
 193. Ozvegy, C., *et al.* Functional characterization of the human multidrug transporter, ABCG2, expressed in insect cells. *Biochemical and biophysical research communications* 285, 111-117 (2001).
 194. Kage, K., *et al.* Dominant-negative inhibition of breast cancer resistance protein as drug efflux pump through the inhibition of S-S dependent homodimerization. *International journal of cancer* 97, 626-630 (2002).
 195. Nakanishi, T., *et al.* Novel 5' untranslated region variants of BCRP mRNA are differentially expressed in drug-selected cancer cells and in normal human tissues: implications for drug resistance, tissue-specific expression, and alternative promoter usage. *Cancer research* 66, 5007-5011 (2006).
 196. Zong, Y., Zhou, S., Fatima, S. & Sorrentino, B.P. Expression of mouse Abcg2 mRNA during hematopoiesis is regulated by alternative use of multiple leader exons and promoters. *The Journal of biological chemistry* 281, 29625-29632 (2006).
 197. Bailey-Dell, K.J., Hassel, B., Doyle, L.A. & Ross, D.D. Promoter characterization and genomic organization of the human breast cancer resistance protein (ATP-binding cassette transporter G2) gene. *Biochimica et biophysica acta* 1520, 234-241 (2001).

198. To, K.K., Zhan, Z. & Bates, S.E. Aberrant promoter methylation of the ABCG2 gene in renal carcinoma. *Molecular and cellular biology* 26, 8572-8585 (2006).
199. Turner, J.G., *et al.* ABCG2 expression, function, and promoter methylation in human multiple myeloma. *Blood* 108, 3881-3889 (2006).
200. Ee, P.L., *et al.* Identification of a novel estrogen response element in the breast cancer resistance protein (ABCG2) gene. *Cancer research* 64, 1247-1251 (2004).
201. Imai, Y., Ishikawa, E., Asada, S. & Sugimoto, Y. Estrogen-mediated post transcriptional down-regulation of breast cancer resistance protein/ABCG2. *Cancer research* 65, 596-604 (2005).
202. Zhang, Y., *et al.* Transcriptional upregulation of breast cancer resistance protein by 17beta-estradiol in ERalpha-positive MCF-7 breast cancer cells. *Oncology* 71, 446-455 (2006).
203. Wang, H., Unadkat, J.D. & Mao, Q. Hormonal regulation of BCRP expression in human placental BeWo cells. *Pharmaceutical research* 25, 444-452 (2008).
204. Wulf, G.G., *et al.* A leukemic stem cell with intrinsic drug efflux capacity in acute myeloid leukemia. *Blood* 98, 1166-1173 (2001).
205. Hirschmann-Jax, C., *et al.* A distinct "side population" of cells with high drug efflux capacity in human tumor cells. *Proceedings of the National Academy of Sciences of the United States of America* 101, 14228-14233 (2004).
206. Brown, M.D., *et al.* Characterization of benign and malignant prostate epithelial Hoechst 33342 side populations. *Prostate* 67, 1384-1396 (2007).
207. Chang, H.Y., *et al.* Robustness, scalability, and integration of a wound-response gene expression signature in predicting breast cancer survival. *Proceedings of the National Academy of Sciences of the United States of America* 102, 3738-3743 (2005).
208. Thiery, J.P. Epithelial-mesenchymal transitions in tumour progression. *Nature reviews* 2, 442-454 (2002).
209. Jonker, J.W., *et al.* Contribution of the ABC transporters Bcrp1 and Mdr1a/1b to the side population phenotype in mammary gland and bone marrow of mice. *Stem cells (Dayton, Ohio)* 23, 1059-1065 (2005).
210. Behbod, F., *et al.* Transcriptional profiling of mammary gland side population cells. *Stem cells (Dayton, Ohio)* 24, 1065-1074 (2006).
211. Larderet, G., *et al.* Human side population keratinocytes exhibit long-term proliferative potential and a specific gene expression profile and can form a pluristratified epidermis. *Stem cells (Dayton, Ohio)* 24, 965-974 (2006).
212. Fried, J., *et al.* Effects of Hoechst 33342 on survival and growth of two tumor cell lines and on hematopoietically normal bone marrow cells. *Cytometry* 3, 42-47 (1982).
213. Holliday, R. & Pugh, J.E. DNA modification mechanisms and gene activity during development. *Science (New York, N.Y)* 187, 226-232 (1975).
214. Riggs, A.D. X inactivation, differentiation, and DNA methylation. *Cytogenet Cell Genet* 14, 9-25 (1975).

215. Ries, C., *et al.* MMP-2, MT1-MMP, and TIMP-2 are essential for the invasive capacity of human mesenchymal stem cells: differential regulation by inflammatory cytokines. *Blood* 109, 4055-4063 (2007).
216. Aguiari, P., *et al.* High glucose induces adipogenic differentiation of muscle-derived stem cells. *Proceedings of the National Academy of Sciences of the United States of America* 105, 1226-1231 (2008).
217. Cunha, G.R., Hayward, S.W., Dahiya, R. & Foster, B.A. Smooth muscle-epithelial interactions in normal and neoplastic prostatic development. *Acta Anat (Basel)* 155, 63-72 (1996).
218. Podlasek, C.A., Barnett, D.H., Clemens, J.Q., Bak, P.M. & Bushman, W. Prostate development requires Sonic hedgehog expressed by the urogenital sinus epithelium. *Dev Biol* 209, 28-39 (1999).
219. Tlsty, T.D. & Hein, P.W. Know thy neighbor: stromal cells can contribute oncogenic signals. *Curr Opin Genet Dev* 11, 54-59 (2001).
220. Shapiro, E., *et al.* Morphometric analysis of pediatric and nonhyperplastic prostate glands: evidence that BPH is not a unique stromal process. *Prostate* 33, 177-182 (1997).
221. Bartsch, G., Muller, H.R., Oberholzer, M. & Rohr, H.P. Light microscopic stereological analysis of the normal human prostate and of benign prostatic hyperplasia. *J Urol* 122, 487-491 (1979).
222. Lin, V.K., *et al.* Prostatic stromal cells derived from benign prostatic hyperplasia specimens possess stem cell like property. *Prostate* 67, 1265-1276 (2007).
223. Ceder, J.A., Jansson, L., Ehrnstrom, R.A., Ronnstrand, L. & Abrahamsson, P.A. The characterization of epithelial and stromal subsets of candidate stem/progenitor cells in the human adult prostate. *Eur Urol* 53, 524-531 (2008).
224. Bergers, G. & Coussens, L.M. Extrinsic regulators of epithelial tumor progression: metalloproteinases. *Curr Opin Genet Dev* 10, 120-127 (2000).
225. Cunha, G.R., Hayward, S.W., Wang, Y.Z. & Ricke, W.A. Role of the stromal microenvironment in carcinogenesis of the prostate. *International journal of cancer* 107, 1-10 (2003).
226. Galie, M., *et al.* Mesenchymal stem cells share molecular signature with mesenchymal tumor cells and favor early tumor growth in syngeneic mice. *Oncogene* 27, 2542-2551 (2008).
227. Karnoub, A.E., *et al.* Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. *Nature* 449, 557-563 (2007).
228. Massague, J., Seoane, J. & Wotton, D. Smad transcription factors. *Genes & development* 19, 2783-2810 (2005).
229. Locklin, R.M., Oreffo, R.O. & Triffitt, J.T. Effects of TGFbeta and bFGF on the differentiation of human bone marrow stromal fibroblasts. *Cell Biol Int* 23, 185-194 (1999).
230. Maeda, S., Hayashi, M., Komiya, S., Imamura, T. & Miyazono, K. Endogenous TGF-beta signaling suppresses maturation of osteoblastic mesenchymal cells. *EMBO J* 23, 552-563 (2004).
231. Massague, J., Blain, S.W. & Lo, R.S. TGFbeta signaling in growth control, cancer, and heritable disorders. *Cell* 103, 295-309 (2000).

232. Seoane, J. Escaping from the TGFbeta anti-proliferative control. *Carcinogenesis* 27, 2148-2156 (2006).
233. Derynck, R., Akhurst, R.J. & Balmain, A. TGF-beta signaling in tumor suppression and cancer progression. *Nature genetics* 29, 117-129 (2001).
234. Siegel, P.M. & Massague, J. Cytostatic and apoptotic actions of TGF-beta in homeostasis and cancer. *Nature reviews* 3, 807-821 (2003).
235. Massague, J. TGFbeta in Cancer. *Cell* 134, 215-230 (2008).
236. Tuxhorn, J.A., McAlhany, S.J., Yang, F., Dang, T.D. & Rowley, D.R. Inhibition of transforming growth factor-beta activity decreases angiogenesis in a human prostate cancer-reactive stroma xenograft model. *Cancer research* 62, 6021-6025 (2002).
237. Rowley, D.R. What might a stromal response mean to prostate cancer progression? *Cancer metastasis reviews* 17, 411-419 (1998).
238. Tuxhorn, J.A., *et al.* Reactive stroma in human prostate cancer: induction of myofibroblast phenotype and extracellular matrix remodeling. *Clin Cancer Res* 8, 2912-2923 (2002).
239. Ao, M., *et al.* Cross-talk between paracrine-acting cytokine and chemokine pathways promotes malignancy in benign human prostatic epithelium. *Cancer research* 67, 4244-4253 (2007).
240. Abdallah, B.M., *et al.* dlk1/FA1 regulates the function of human bone marrow mesenchymal stem cells by modulating gene expression of pro-inflammatory cytokines and immune response-related factors. *The Journal of biological chemistry* 282, 7339-7351 (2007).
241. Ceder, J.A., Jansson, L., Helczynski, L. & Abrahamsson, P.A. Delta-Like 1 (Dlk-1), a Novel Marker of Prostate Basal and Candidate Epithelial Stem Cells, Is Downregulated by Notch Signalling in Intermediate/Transit Amplifying Cells of the Human Prostate. *Eur Urol* (2008).
242. Meyer-Siegler, K.L., Bellino, M.A. & Tannenbaum, M. Macrophage migration inhibitory factor evaluation compared with prostate specific antigen as a biomarker in patients with prostate carcinoma. *Cancer* 94, 1449-1456 (2002).
243. Meyer-Siegler, K.L., Iczkowski, K.A. & Vera, P.L. Further evidence for increased macrophage migration inhibitory factor expression in prostate cancer. *BMC Cancer* 5, 73 (2005).
244. Meyer-Siegler, K.L., Iczkowski, K.A., Leng, L., Bucala, R. & Vera, P.L. Inhibition of macrophage migration inhibitory factor or its receptor (CD74) attenuates growth and invasion of DU-145 prostate cancer cells. *J Immunol* 177, 8730-8739 (2006).
245. Conrad, C., *et al.* Alkaline phosphatase, glutathione-S-transferase-P, and cofilin-1 distinguish multipotent mesenchymal stromal cell lines derived from the bone marrow versus peripheral blood. *Stem Cells Dev* 17, 23-27 (2008).
246. Thalmann, G.N., *et al.* Androgen-independent cancer progression and bone metastasis in the LNCaP model of human prostate cancer. *Cancer research* 54, 2577-2581 (1994).
247. Wu, H.C., *et al.* Derivation of androgen-independent human LNCaP prostatic cancer cell sublines: role of bone stromal cells. *International journal of cancer* 57, 406-412 (1994).

248. Wu, T.T., *et al.* Establishing human prostate cancer cell xenografts in bone: induction of osteoblastic reaction by prostate-specific antigen-producing tumors in athymic and SCID/bg mice using LNCaP and lineage-derived metastatic sublines. *International journal of cancer* 77, 887-894 (1998).
249. Thalmann, G.N., *et al.* LNCaP progression model of human prostate cancer: androgen-independence and osseous metastasis. *Prostate* 44, 91-103 Jul 101;144(102) (2000).
250. Ozen, M., *et al.* Specific histologic and cytogenetic evidence for in vivo malignant transformation of murine host cells by three human prostate cancer cell lines. *Oncol Res* 9, 433-438 (1997).
251. Pathak, S., *et al.* Can cancer cells transform normal host cells into malignant cells? *British journal of cancer* 76, 1134-1138 (1997).
252. Olumi, A.F., Dazin, P. & Tlsty, T.D. A novel coculture technique demonstrates that normal human prostatic fibroblasts contribute to tumor formation of LNCaP cells by retarding cell death. *Cancer research* 58, 4525-4530 (1998).
253. Miura, M., *et al.* Accumulated chromosomal instability in murine bone marrow mesenchymal stem cells leads to malignant transformation. *Stem cells (Dayton, Ohio)* 24, 1095-1103 (2006).
254. Wu, C., *et al.* Side population cells isolated from mesenchymal neoplasms have tumor initiating potential. *Cancer research* 67, 8216-8222 (2007).
255. Phinney, D.G. & Prockop, D.J. Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair--current views. *Stem cells (Dayton, Ohio)* 25, 2896-2902 (2007).
256. Sell, S. Stem cell origin of cancer and differentiation therapy. *Crit Rev Oncol Hematol* 51, 1-28 (2004).
257. Cho, J.J., *et al.* Enzymatically labeled chromosomal probes for in situ identification of human cells in xenogeneic transplant models. *Nature medicine* 8, 1033-1036 (2002).
258. Stroun, M., *et al.* Neoplastic characteristics of the DNA found in the plasma of cancer patients. *Oncology* 46, 318-322 (1989).
259. Bennett, P.R., *et al.* Prenatal determination of fetal RhD type by DNA amplification. *The New England journal of medicine* 329, 607-610 (1993).
260. Darwin, C.R. *On the origin on species by means of natural selection, or the preservation of favoured races in the struggle for life*, (John Murray, 1859).
261. Harris, A.L. Hypoxia--a key regulatory factor in tumour growth. *Nature reviews* 2, 38-47 (2002).
262. Cipolleschi, M.G., Dello Sbarba, P. & Olivotto, M. The role of hypoxia in the maintenance of hematopoietic stem cells. *Blood* 82, 2031-2037 (1993).
263. Krishnamurthy, P., *et al.* The stem cell marker Bcrp/ABCG2 enhances hypoxic cell survival through interactions with heme. *The Journal of biological chemistry* 279, 24218-24225 (2004).
264. Martin, C.M., *et al.* Hypoxia-inducible factor-2alpha transactivates Abcg2 and promotes cytoprotection in cardiac side population cells. *Circ Res* 102, 1075-1081 (2008).

265. Simon, M.C. & Keith, B. The role of oxygen availability in embryonic development and stem cell function. *Nat Rev Mol Cell Biol* 9, 285-296 (2008).
266. Huntly, B.J. & Gilliland, D.G. Leukaemia stem cells and the evolution of cancer-stem-cell research. *Nature reviews* 5, 311-321 (2005).
267. Krivtsov, A.V., *et al.* Transformation from committed progenitor to leukaemia stem cell initiated by MLL-AF9. *Nature* 442, 818-822 (2006).
268. Comerford, K.M., *et al.* Hypoxia-inducible factor-1-dependent regulation of the multidrug resistance (MDR1) gene. *Cancer research* 62, 3387-3394 (2002).
269. Nishi, H., *et al.* Hypoxia-inducible factor 1 mediates upregulation of telomerase (hTERT). *Molecular and cellular biology* 24, 6076-6083 (2004).
270. Danet, G.H., Pan, Y., Luongo, J.L., Bonnet, D.A. & Simon, M.C. Expansion of human SCID-repopulating cells under hypoxic conditions. *The Journal of clinical investigation* 112, 126-135 (2003).
271. Morrison, S.J., *et al.* Culture in reduced levels of oxygen promotes clonogenic sympathoadrenal differentiation by isolated neural crest stem cells. *J Neurosci* 20, 7370-7376 (2000).
272. Studer, L., *et al.* Enhanced proliferation, survival, and dopaminergic differentiation of CNS precursors in lowered oxygen. *J Neurosci* 20, 7377-7383 (2000).
273. Genbacev, O., Zhou, Y., Ludlow, J.W. & Fisher, S.J. Regulation of human placental development by oxygen tension. *Science (New York, N.Y)* 277, 1669-1672 (1997).
274. Axelson, H., Fredlund, E., Ovenberger, M., Landberg, G. & Pahlman, S. Hypoxia-induced dedifferentiation of tumor cells--a mechanism behind heterogeneity and aggressiveness of solid tumors. *Semin Cell Dev Biol* 16, 554-563 (2005).
275. Takahashi, K. & Yamanaka, S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 126, 663-676 (2006).
276. Wernig, M., *et al.* In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state. *Nature* 448, 318-324 (2007).
277. Park, I.H., *et al.* Reprogramming of human somatic cells to pluripotency with defined factors. *Nature* 451, 141-146 (2008).
278. Glinskii, A.B., *et al.* Viable circulating metastatic cells produced in orthotopic but not ectopic prostate cancer models. *Cancer research* 63, 4239-4243 (2003).
279. Li, L. & Neaves, W.B. Normal stem cells and cancer stem cells: the niche matters. *Cancer research* 66, 4553-4557 (2006).
280. Van Dyke, T. & Jacks, T. Cancer modeling in the modern era: progress and challenges. *Cell* 108, 135-144 (2002).
281. Bruchovsky, N., *et al.* Final results of the Canadian prospective phase II trial of intermittent androgen suppression for men in biochemical recurrence after radiotherapy for locally advanced prostate cancer: clinical parameters. *Cancer* 107, 389-395 (2006).
282. Akakura, K., *et al.* Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen. *Cancer* 71, 2782-2790 (1993).

283. Bruchovsky, N., *et al.* Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma. *Cancer research* 50, 2275-2282 (1990).
284. Akakura, K., *et al.* Effects of intermittent androgen suppression on the stem cell composition and the expression of the TRPM-2 (clusterin) gene in the Shionogi carcinoma. *J Steroid Biochem Mol Biol* 59, 501-511 (1996).
285. Huss, W.J., Gray, D.R., Greenberg, N.M., Mohler, J.L. & Smith, G.J. Breast cancer resistance protein-mediated efflux of androgen in putative benign and malignant prostate stem cells. *Cancer research* 65, 6640-6650 (2005).
286. Popper, K.R. *Logik der Forschung*, (Julius Springer, 1934).
287. Check, E. Stem cells: the hard copy. *Nature* 446, 485-486 (2007).
288. Triel, C., Vestergaard, M.E., Bolund, L., Jensen, T.G. & Jensen, U.B. Side population cells in human and mouse epidermis lack stem cell characteristics. *Experimental cell research* 295, 79-90 (2004).
289. Zhu, X., *et al.* Dynamic regulation of estrogen receptor-beta expression by DNA methylation during prostate cancer development and metastasis. *The American journal of pathology* 164, 2003-2012 (2004).
290. Esteller, M. Cancer epigenomics: DNA methylomes and histone-modification maps. *Nat Rev Genet* 8, 286-298 (2007).
291. Pantoja, C., de Los Rios, L., Matheu, A., Antequera, F. & Serrano, M. Inactivation of imprinted genes induced by cellular stress and tumorigenesis. *Cancer research* 65, 26-33 (2005).
292. Lemaire, M., *et al.* Importance of dose-schedule of 5-aza-2'-deoxycytidine for epigenetic therapy of cancer. *BMC Cancer* 8, 128 (2008).
293. Maslow, A. *Motivation and personality*, (1954).
294. Rosal, R. *¿Qué nos humaniza? ¿Qué nos deshumaniza?*, (Bilbao, 2003).
295. Hume, D. *Philosophical essays concerning human understanding*, (1748).

Altres obres consultades:

Carroll, P.R., Grossfeld, G.D. *Prostate cancer* (BC Decker, 2002)

Gould, S.J. *The structure of evolutionary theory* (Belknap, Harvard, 2002)

Pujol, J.M., Solà J., *Ortotipografia Manual de l'editor, l'autoeditor i el disenyador gràfic* (Columna assaig, Eines 3, 1995)