

REFERENCES

- Adams, J., Carder, P.J., Downey, S., *et al.* (2000). Vascular endothelial growth factor (VEGF) in breast cancer: comparison of plasma, serum, and tissue VEGF and microvessel density and effects of tamoxifen. *Cancer Res.*, 60, 2898-2905.
- Albini, A., Fontanini, G., Masiello, L., *et al.* (1994). Angiogenic potential in vivo by Kaposi's sarcoma cell-free supernatants and HIV-1 tat product: inhibition of KS-like lesions by tissue inhibitor of metalloproteinase-2. *AIDS.*, 8, 1237-1244.
- Appleby, S.B., Ristimaki, A., Neilson, K *et al.* (1994). Structure of the human cyclooxygenase-2 gene. *Biochem.J.*, 302, 723-727.
- Aprelikova, O., Pajusola, K., Partanen, J., *et al.* (1992). *FLT4*, a novel class III receptor tyrosine kinase in chromosome 5q33-qter. *Cancer Res.*, 52, 746-748.
- Arbiser, J.L. (1997). Antiangiogenic therapy and dermatology: a review. *Drugs Today*, 33, 687-696.
- Arbiser, J.L., Klauber, N., Rohan, R., *et al.* (1998). Curcumin is an *in vivo* inhibitor of angiogenesis. *Mol.Med.*, 4, 376-383.
- Ben-Av, P., Crofford, L.J., Wilder, R.L., *et al.*, (1995). Induction of vascular endothelial growth factor expression in synovial fibroblasts by prostaglandin E and interleukin-1: a potential mechanism for inflammatory angiogenesis. *FEBS.Lett.*, 372 (1), 83-7.
- Bian, X.W., Du L.L., Shi JQ, *et al.* (2000). Correlation of bFGF, FGFR-1 and VEGF expression with vascularity and malignancy of human astrocytomas. *Anal.Quant.Cytol.Histol.*, 22, 267-274.
- Biglar, S.A., Deering, R.E., and Brawer, M.K. (1993). Comparison of microscopic vascularity in benign and malignant prostate tissue. *Hum.Pathol.*, 24, 220-226.
- Boolbol, S.K., Dannenberg, A.J., Chadburn, A., *et al.* (1996). Cyclooxygenase-2 overexpression and tumor formation are blocked by sulinac in a murine model of familial adenomatous polyposis. *CancerRes.*, 56, 2556-2560.
- Bouck, N., Stellmach, V. and Hsu, S., (1996). How tumors become angiogenic. *Adv.Cancer Res.*, 69, 135-174.

- Breier, G. (2000). Angiogenesis in embryonic development—a review. *Placenta*, 21, Suppl. A, S11-S15.
- Broll, R., Erdmann, H., Duchrow, M., *et al.* (2001). Vascular endothelial growth factor (VEGF)-a valuable serum tumour marker in patients with colorectal cancer. *Eur J Surg Oncol.*, 27, 37-42.
- Buckman, S.Y., Gresham, A., Hale, P., *et al.* (1998). COX-2 expression is induced by UVB exposure in human skin : implications for the development of skin cancer. *Carcinogenesis.*, 19, 723-729.
- Bussolino, F., Mantovani, A. and Persico, G. (1997). Molecular mechanism of blood vessel formation. *Trends Biochem.Sci.*, 22, 251-256.
- Carmeliet, P. and Jain, R.K. (2000). Angiogenesis in cancer and other diseases. *Nature*, 407, 249-257.
- Caughey, G.E., Cleland, L.G., Penglis, P.S., *et al.* (2001). Role of cyclooxygenase (COX)-1 and COX-2 in prostanoid production by human endothelial cells: selective upregulation of prodtacyclin synthesis by COX-2. *J.Immunol.*, 167, 2831-2838.
- Chen, C.C., Sun, Y.T., Chen, J.J., *et al.* (2001). Tumor necrosis factor- α -induced cyclooxygenase-2 expression via sequential activation of ceramide-dependent mitogen-activated protein kinases, and I κ B kinase $\frac{1}{2}$ in human alveolar epithelial cells. *Mol. Pharmacol.*, 59, 493-500.
- Cheng, A.L., Lin, J.K., Hsu, M.M., *et al.* (1998). Phase I chemoprevention clinical trial of curcumin. *Proc.Am.Soc.Clin.Oncol.*, 17, 558.
- Chen, C.M. and Fang, H.C. (1997). Chemical analysis of the active principles of *Curcuma* species. In: *Modern Treatise on Chinese Herbal Medicines*, Vol. III, pp. 95-105 (Sung, C.Y., Chou, D.W., Fung, C.J. and Zhao, H.M., *Eds.*), Institute of Pharmaceutical Sciences, MedicalAcademia, Beijing, P.R.C.
- Cheng, A.S., Chan, H.L., To, K.F., *et al.* (2004). Cyclooxygenase-2 pathway correlates with vascular endothelial growth factor expression and tumor angiogenesis in hepatitis B virus-associate hepatocellular carcinoma. *Int.J.Oncol.*, 24 (4), 853-860.
- Chin, L., Tam, A., Pomerantz, J., *et al.* (1999). Essential role for oncogenic Ras in tumour maintenance. *Nature*, 400, 468-472.

- Cianchi, F., Cortesini, C., Bechi, P., *et al.* (2001). Up-regulation of cyclooxygenase 2 gene expression correlates with tumor angiogenesis in human colorectal cancer. *Gastroenterology*, 121, 1339-1347.
- Cockerill, G.W., Gambel, J.R. and Vadas, M.A., (1995). Angiogenesis: models and modulators. *Int.Rev.Cytol.*, 159, 113-160.
- Dameron, K.M., Volpert, O.V., Tainsky, M.A., *et al.* (1994). Control of angiogenesis in fibroblasts by p53 regulation of thrombospondin-1. *Science.*, 265, 1582-1584.
- Daniel, T.O., Liu, H., Morrow, J.D., *et al.* (1999). Thromboxane A2 is a mediator of cyclooxygenase-2-dependent endothelial migration and angiogenesis. *Cancer Res.*, 59, 4574-4577.
- Davies, G., Martin, L-A., Sacks, N., *et al.*, (2002). Cyclooxygenase-2(COX-2), aromatase and breast cancer: a possible role for COX-2 inhibitors in breast cancer chemoprevention. *Annals of Oncology*, 13, 669-678.
- Dewitt, D.L and Smith, W.L. (1988). Primary structure of prostaglandin G/H synthase from sheep vesicular gland determined from the complementary DNA sequence. *Proc.Natl.Acad.Sci.USA.*, 85, 1412-1416.
- Dimmerler, S., Fleming, I., Fisslthaler, B., *et al.* (1999). Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation *Nature*, 399, 601-605.
- Dixon, D.A., Kaplan, C.D., McIntyre, T.M., *et al.* (2000). Post-transcriptional control of cyclooxygenase-2 gene expression. The role of the 3'-untranslated region. *J.Biol.Chem.*, 275, 11750-11757.
- Dormond, O., Foletti, A., Paroz, C., *et al.* (2001) NSAIDs inhibit α V β 3 integrin-mediated and Cdc42/Rac-dependent endothelial-cell spreading, migration and angiogenesis. *Nature*, 7, 1041-1047.
- DuBois, R.N., Awad, J., Morrow, J., *et al.* (1994). Regulation of eicosanoid production and mitogenesis in rat intestinal epithelial cells by transforming growth factor- α and phorbol ester. *J.Clin.Investg.*, 93, 493-498.
- DuBois, R.N., Radhika, A., Reddy, B.S., *et al.* (1996). Increased cyclooxygenase-2 levels in carcinogen-induced rat colonic tumors. *Gastroenterology*, 110, 1259-1262.

- Eberhart, C.E., Coffey, R.J., Radhika, A., *et al.* (1994). Up-regulation of cyclooxygenase-2 gene expression in human colorectal adenomas and adenocarcinomas. *Gastroenterology*, 107, 1183-1188.
- Ellis, L.M., Takanashi, Y., Liu, W., *et al.* (2000). Vascular endothelial growth factor in human colon cancer: biology and therapeutic implications. *Oncologist*, 5 (suppl 1), 11-15.
- Esser, S., Lampugnani, M.G., Coroda, M., *et al.*, (1998). Vascular endothelial growth factor induces VE-cadherin tyrosine phosphorylation in endothelial cells. *J.Cell Sci.*, 111, 1853-1865.
- Fava, R.A., Olsen, N.J., Spencer-Green, G., *et al.* (1994). Vascular permeability factor/endothelial growth factor (VPF/VEGF): accumulation and expression in human synovial fluids and rheumatoid synovial tissue. *J.Exp.Med.*, 180, 340-346.
- Ferrara, N. and Davis-Smyth, T. (1997). The biology of vascular endothelial growth factor. *Endocrine Reviews*, 18, 4-25.
- Ferrara, N. (1999). Vascular endothelial growth factor: molecular and biological aspects. *Curr. Top. Microbiol. Immunol.*, 237, 1-30.
- Ferrara, N. (2000). Vascular endothelial growth factor and the regulation of angiogenesis. *Recent Prog.Horm.Res.*, 55, 15-35.
- Ferrara, N., (2001). Role of vascular endothelial growth factor in regulation of physiological angiogenesis. *Am.J.Physiol.*, 280, C1358-1366.
- Flaumenhaft, R. and Rifkin, D.B. (1992). The extracellular regulation of growth factor action. *Mol.Biol.Cell.*, 3, 1057-1065.
- Folkman, J. (1971). Tumor angiogenesis: therapeutic implications. *N.Engl.J.Med.*, 285, 1182-6.
- Folkman, J. (1972). Anti-angiogenesis: new concept for therapy of solid tumors. *Ann.Surg.*, 175, 409-16.
- Folkman, J. (1990). What is the evidence that tumors are angiogenesis dependent? *J Natl.Cancer Inst.*, 82, 4-6.
- Folkman, J. (1996). Fighting cancer by attacking its blood supply. *Sci.Am.*, 275, 150-4.
- Folkman, J. and Shing, J. (1992). Angiogenesis. *J.Biol.Chem.*, 267, 10931-10934.

- Fortes, Z.B., Oliveira, M.A., Scivolett, R., *et al.* (1990). Nitric oxide release may be involved in the microcirculatory response to acetylcholine. *EPJ.*, 182, 143-147.
- Freireich, E.J., Gehan, E.A., Rall, D.P., *et al.* (1966). Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey and man. *Cancer Chemother.Rep.*, 50, 219-244.
- Fujio, Y. and Walsh, K. (1999). Akt mediates cytoprotection of endothelial cells by vascular endothelial growth factor an anchorage-dependent manner. *J.Biol.Chem.*, 274,16349-16354.
- Fulton, D., Gratton, J.P., McCabe, T.J., *et al.* (1999). Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. *Nature*, 399, 597-601.
- Galardy, R.E., Grobelny, D., Foellmer, H.G., *et al.* (1994). Inhibition of angiogenesis by the matrix metalloproteinase inhibitor N-[2R-2(Hydroxamidocarbonylmethyl)-4-methylpentanoyl]-L-tryptophan methylamide. *Cancer Res.*, 54, 4715-4718.
- Galland, F., Karamysheva, A., Mattei, M-G., *et al.* (1992). Chromosomal localization of *FLT4*, a novel receptor-type tyrosine kinase gene. *Genomics*, 13, 475-478.
- Gallo, O., Franchi, A., Magnelli, L., *et al.* (2001). Cyclooxygenase-2 pathway correlates with VEGF expression in head and neck cancer. Implications for tumor angiogenesis and metastasis. *Neoplasia*, 3, 1-9.
- Garcia-Cardena, G and Folkman, J. (1998). Is there a role for nitric oxide in tumor angiogenesis? *J.Natl.Cancer.Inst.*, 90, 560-561.
- Geber, H.P., McMurtrey, A., Kowalski, J., *et al.* (1998). Vascular endothelial growth factor regulates endothelial cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway. Requirement for Flk-1/KDR activation. *J.Biol.Chem.*, 273, 30336-30343.
- Gess, B. Sandner, P., Kurtz, A. (1996). Differential effects of kinase inhibitors on erythropoietin and vascular endothelial growth factor gene expression in rat hepatocytes. *Pflugers Arch.*, 432, 426-432.
- Ghatak, N., and Basu, N. (1972). Sodium curcumin as an effective anti-inflammatory agent. *Ind.J.Exp.Biol.* 10:235.

- Gierse, J.K., Hauser, S.D., Creely, D.P., *et al.* (1995). Expression and selective inhibition of the constitutive and inducible forms of human cyclooxygenase. *Biochem.J.*, 305, 479-484.
- Gilhooly, E.M. and Rose, D.P. (1999). The association between a mutated *ras* gene and cyclooxygenase-2 expression in human breast cancer cell lines. *Int.J.Oncol.*, 15, 267-270.
- Goel, A., Boland, C.R., and Chauhan, D.P. (2001). Specific inhibition of cyclooxygenase-2 (COX-2) expression by dietary curcumin in HT-29 human colon cancer cells. *Cancer Lett.*, 172, 111-118.
- Guerin, M., Sheng, Z.M., Andrieu, N., *et al.* (1990). Strong association between *c-myc* and oestrogen-receptor expression in human breast cancer. *Oncogene.*, 5, 131-135.
- Gunsilius, E., Tschmelitsch, J., Eberwein, M., *et al.* (2002). In vivo release of vascular endothelial growth factor from colorectal carcinomas. *Oncology*, 62, 313-317.
- Gupta, M.K. and Qin Ren-Yi. (2003). Mechanism and its regulation of tumor-induced angiogenesis. *World J.Gastroenterol.*, 9 (6), 1144-1155.
- Gururaj, A.E., Belakavadi, M., Venkatesh, D.A., *et al.* (2002). Molecular mechanisms of anti-angiogenic effect of curcumin. *Biochem.Biophys.Res. Commun.*, 297, 934-942.
- Hamasaki, Y., Kitzler, J., Hardman, R., *et al.* (1993). Phorbol ester and epidermal growth factor enhance the expression of two inducible prostaglandin H synthase genes in rat tracheal epithelial cells. *Arch.Biochem.Biophys.*, 304, 226-234.
- Hanahan, D. and Folkman, J. (1996). Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell*, 86, 353-364.
- Hanahan, D. and Weinberg, R.A. (2000). The hallmarks of cancer. *Cell*, 100, 57-70.
- Harmey, J.H., Dimitriadis, E., Kay, E., *et al.*, (1998). Regulation of macrophage production of vascular endothelial growth factor (VEGF) by hypoxia and transforming growth factor beta-1. *Ann.Surg.Oncol.*, 5, 271-278.
- Herschman, H.R. (1994). Regulation of prostaglandin synthase-1 and prostaglandin synthase-2. *Cancer.Metastasis Rev.*, 13, 241-256.

- Hida, T., Yatabe, Y., Achiwa, H., *et al.* (1998). Increased expression of cyclooxygenase -2 occurs frequently in human lung cancers, specifically in adenocarcinomas. *Cancer Res.*, 58, 3761-3764.
- Hideyasu, O., Takagi, H., Suzuma, K., *et al.* (1999). Hypoxia and vascular endothelial growth factor selectively upregulate angiopoietin-2 in bovine microvascular endothelial cells. *J.Biol.Chem.*, 274, 15732-15739.
- Hirai M, Nakagawara A, Oosaki T, *et al.* (2001). Expression of vascular endothelial growth factors (VEGF-A/VEGF-1 and VEGF-C/VEGF-2) in postmenopausal uterine endometrial carcinoma. *Gynecol.Oncol.*, 80, 181-188.
- Hla, T. and Neilson, K. (1992). Human cyclooxygenase-2 cDNA. *Proc.Natl.Acad.Sci. U.S.A.*, 89, 7384-7388.
- Horak, E.R., Leek, R., Klenk, N., *et al.* (1992). Quantitative angiogenesis assessed by anti-PECAM antibodies: correlation with node metastasis and survival in breast cancer. *Lancet*, 340, 1120-1124.
- Huang, M.T., Smart, R.C., Wong, C.Q., *et al.* (1988). Inhibitory effect of curcumin, chlorogenic acid, caffeic acid and ferulic acid on tumor promotion in mouse skin by 12-O-tetradecanoylphorbol-13-acetate. *Cancer Res.*, 48:5941-5946.
- Huang, M.T., Lysz, T., Ferraro, T., *et al.* (1991). Inhibitory effects of curcumin *in vivo* lipoxygenase and cyclooxygenase activities in mouse epidermis. *Cancer Res.*, 51:813-819.
- Huang, M.T., Wang, Z.Y., Georgiadis, C.A., *et al.* (1992). Inhibitory effect of curcumin on tumor initiation by benzo[a] pyrene and 7,12-dimethylbenz[a]anthracene. *Carcinogenesis.*, 13, 2183-2186.
- Huang, M.T., Lou, Y.R., Ma, W., *et al.* (1994). Inhibitory effects of dietary curcumin on forestomach, duodenal and colon carcinogenesis in mice. *Cancer Res.*, 54, 5841-5847.
- Huang, M.T., Ma, W., Lu, Y.P., *et al.* (1995). Effect of curcumin, demethoxycurcumin, bisdemethoxy-curcumin and tetrahydrocurcumin on TPA-induced tumor promotion. *Carcinogenesis.*, 16, 2493-2497.
- Huang, M.T., Ma, W., Yen, P., *et al.* (1997). Inhibitory effects of topical application of low doses of curcumin on TPA-induced tumor promotion and oxidized DNA bases in mouse epidermis. *Carcinogenesis.*, 18, 83-88.

- Illi, B., Puri, P., Morgante, M.C., *et al.* (2000). Nuclear factor- κ B and camp response element binding protein mediate opposite transcriptional effects on the Flk-1/KDR gene promoter. *Circ.Res.*, 86, E110-117.
- Ireson, C., Orr, S., Jones, D.J.L., *et al.* (2001). Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes, and in the rat *in vivo*, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E₂ production. *Cance.Res.*, 61, 1058-1064.
- Iruela-Arispe, M.L. and Dvorak, H.F. (1997) Angiogenesis: a dynamic balance of stimulators and inhibitors. *Throm.Haemost.*, 78, 672-677.
- Ishigami, S.I., Arai, A., Furutani, M., *et al.* (1998). Predictive value of vascular endothelial growth factor (VEGF) in metastasis and prognosis of human colorectal cancer. *Br.J.Cancer.*, 78, 1379-1384.
- Jiang, B.H., Agani, F., Passaniti, A. *et al.* (1997). V-SRC induces expression of hypoxia-inducible factor 1 (HIF-1) and transcription of genes encoding vascular endothelial growth factor and enolase 1: involvement of HIF-1 in tumor progression. *Cancer.Res.*, 57, 5328-5335.
- Johnson, M.D., Kim, H-RC., Chesler, L., *et al.* (1994). Inhibition of angiogenesis by tissue inhibitor of metalloproteinases. *J.Cell Physiol.*, 160, 194-202.
- Jones, D.A., Carlton, D.P., McIntyre, T.M., *et al.* (1993). Molecular cloning of human prostaglandin endoperoxide synthase type II and demonstration of expression in response to cytokines. *J.Biol.Chem.*, 268, 9049-9054.
- Jones, M.K., Wang, H., Peskar, B.M., *et al.* (1999). Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs: insight into mechanisms and implications for cancer growth and ulcer healing. *Nat.Med.*, 5, 1418-1423.
- Jovanovic, S.V., Steenken, S., Boone, C.W., *et al.* (1999). H-atom transfer is a preferred antioxidant mechanism of curcumin. *J.Am.Chem.Soc.*, 121, 9677-9681.
- Kambayashi, T., Alexander, A.R., Fong, M., *et al.* (1995). Potential involvement of IL-10 in suppressing tumour-associated macrophages. Colon-26-derived prostaglandin E₂ inhibits TNF- α release via a mechanism involving IL-10. *J.Immunol.*, 154, 3383-3390.
- Kang, S.M., Maeda, K., Onoda, N., *et al.* (1997). Combined analysis of p53 and vascular endothelial growth factor expression in colorectal carcinoma for

- determination of tumour vascularity and liver metastasis. *Int.J.Cancer.*, 74, 502-507.
- Kasdish, J.I., Butterfield, C.E. and Folkman J. (1979). The effect of fibrin on cultured vascular endothelial cells. *Tissue.Cell.*, 11, 99-108.
- Kawamori, T., Lubet, R., Steele, V.E., *et al.* (1999). Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. *Cancer.Res.*, 59, 597-601.
- Kelloff, G.J., Hawk, E.T., Karp, J.E., *et al.* (1997). Progress in clinical chemoprevention. *Semin.Oncol.*, 24, 241-252.
- Kerbel, R.S. (1997). A cancer therapy resistant to resistance. *Nature (Lond.)*, 390, 335-6.
- Kerbel, R.S., Vitoria-Petit, A., Okada, F., *et al.* (1998). Establishing a link between oncogenes and tumor angiogenesis. *Mol.Med.*, 4, 286-295.
- Kerbel, R.S. (2000). Tumor angiogenesis: past, present, and the near future. *Carcinogenesis*, 21, 505-515.
- Kevil, C.G., Payne, D.K., Mire, E., *et al.*, (1998). Vascular permeability factor/vascular endothelial cell growth factor-mediated permeability occurs through disorganization of endothelial junctional proteins. *J.Biol.Chem.*, 273, 15099-15103.
- Khwaja, A. (1999). Akt is more than just a Bad kinase. *Nature*, 401, 33-34.
- Kim, K.J., Li, B., Winer, J., Armanini, M., *et al.* (1993). Inhibition of vascular endothelial growth factor-induced angiogenesis suppress tumor growth *in vivo*. *Nature*, 362, 841-844.
- Koki, A.T., Leahy, K.M. and Masferrer, J.L. (1999). Potential utility of COX-2 inhibitors in chemoprevention and chemotherapy. *Expert.Opin.Investing Drugs*, 8, 1623-1638.
- Kohn, S., Nagy, J.A., Dvorak, H.F., *et al.*, (1992). Pathways of macro-molecular tracer transport across venules and small veins. Structural basis for the hypermeability of tumor blood vessels. *Lab.Invest.*, 67, 596-607.
- Komi, Y., Nakano, A., Niimi, H., *et al.*, (*in press*). Capillary angiogenesis and remodeling induced in rat limb by arteriovenous shunting. *Clin.Hemorheol.Microcirc.*, (*in press*).

- Kondo, A., Asano, M., Matsuo, K., *et al.* (1994). Vascular endothelial growth factor/vascular permeability factor is detectable in the sera of tumor bearing mice and cancer patients. *Biochim.Biophys.Acta.*, 1221, 211-214.
- Koong, A.C., Chen, E.Y., and Giaccia, A.J. (1994). Hypoxia causes the activation of nuclear factor κ B through the phosphorylation of I κ B α on tyrosine residues. *Cancer Res.*, 74, 679-686.
- Kremer, C., Breier, G., Risau, W., *et al.* (1997). Up-regulation of flk-1/vascular endothelial growth factor receptor 2 by its ligand in a cerebral slice culture system. *Cancer Res.*, 57, 3852-3859.
- Krishnaswamy, K. and Raghuramulu, R. (1998). Bioactive Phytochemicals with emphasis on dietary practices. *Indian J.Med.Res.*, 108, 167-181.
- Kumar, H., Heer, K., McDonald, A., *et al.* (1998). Preoperative serum vascular endothelial growth factor can predict stage in colorectal cancer. *Clin. Cancer Res.*, 4, 1279-1285.
- Kunchandy, E. and Rao, M.N.A. (1990). Oxygen radical scavenging activity of curcumin. *Int'l.J.Pharm.*, 38, 239-240.
- Laemmli UK. (1970). Cleavage of structural proteins during the assembly of the head of bacteriophage T₄. *Nature*, 227, 680-684.
- Lal, B.K., Varma, S., Pappas, P.J., *et al.*, (2001). VEGF increases permeability of the endothelial cell monolayer by activation of PKB/akt, endothelial nitric-oxide synthase, and MAP kinase pathways. *Microvas.Res.*, 62, 252-262.
- Leahy, K.M., Ornberg, R. L., Wang, Y., *et al.*, (2002). Cyclooxygenase-2 inhibition by celecoxib reduces proliferation and induces apoptosis in angiogenic endothelial cells *in vivo*. *Cancer Res.*, 62, 2343-2346.
- Lee, S.H., Soyoola, E., Chanmugam, P., *et al.* (1992). Selective expression of mitogen-inducible cyclooxygenase in macrophages stimulated with lipopolysaccharide. *J.Biol.Chem.*, 267, 25934-25938.
- Lehr, H., Leunig, M., Menger, M.D., *et al.* (1993). Dorsal skinfold chamber technique for intravital microscope in nude mice. *Am.J.Pathol.*, 143, 1055-1062.
- Leunig, M., Yuan, F., Menger, M.D., *et al.* (1992). Angiogenesis, microvascular architecture, microhemodynamics, and interstitial fluid pressure during early

- growth of human adenocarcinoma LS174T in SCID mice. *Cancer Res.*, 52, 6553-6560.
- Liotta, L.A., Kleinerman, J. and Saidel, G.M. (1974). Quantitative relationships of intravascular tumor cells, tumor vessels, and pulmonary metastases following tumor implantation. *Cancer Res.*, 34, 997-1004.
- Liu, Y., Cox, S.R. and Morita, T., *et al.* (1995). Hypoxia regulates vascular endothelial growth factor gene expression in endothelial cells. *Circ Res.*, 77, 638-645.
- Liu, X.H., Kirschenbaum, A., Yao, S., *et al.* (2000). Inhibition of cyclooxygenase-2 suppresses angiogenesis and the growth of prostate cancer in vivo. *J.Urol.*, 164, 820-825.
- Loncaster, J.A., Cooper, R.A., Logue, J.P., *et al.* (2000). Vascular endothelial growth factor (VEGF) expression is a prognostic factor for radiotherapy outcome in advanced carcinoma of the cervix. *Br.J.Cancer*, 83, 620-625.
- Lowry, O.H., Rosebrough, N.J., Farr, A.L., *et al.* (1951). Protein measurement with the Folin Phenol reagent. *J.Biol.Chem.*, 193, 265-275.
- Luo, J.C., Yamaguchi, S., Shinkai, A., *et al.* (1998). Significant expression of vascular endothelial growth factor/vascular permeability factor in mouse ascites tumors. *Cancer Res.*, 58, 2652-2660.
- Macchiarini, P., Fontanini, G., Hardin, M.J., *et al.* (1992) Relation of neovascularization to metastasis on non-small cell lung carcinoma. *Lancet*, 340, 145-146.
- Mancuso, P., Burlini, A., Pruneri, G., *et al.* (2001). Resting and activated endothelial cells are increased in the peripheral blood of cancer patients. *Blood*, 97, 3658-3661.
- Mandriota, S.J., Seghezzi, G., Vassalli, J.D., *et al.* (1995). Vascular endothelial growth factor increases urokinase receptor expression in vascular endothelial cell. *J.Biol.Chem.*, 270, 9709-9716.
- Masferrer, J.L., Leahy, K.M., Koki, A.T., *et al.* (2000). Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. *Cancer Res.*, 60:1306-1311.
- McLaren, J., Prentice, A., Charmock-Jones, D.S., *et al.* (1996) Vascular endothelial growth factor is produced by peritoneal fluid macrophages in endometriosis and is regulated by ovarian steroids. *J.Clin.Invest.* 98, 482-489.

- Mellilo, G., Musso, T., Sica, A., *et al.* (1995). A hypoxia-responsive element mediates a novel pathway of activation of the inducible nitric oxide synthase promoter. *J.Exp.Med.*, 182, 1683-1693.
- Mestre, J.R., Mackrell, P.J., Rivadeneira, D.E., *et al.* (2001). Redundancy in the signaling pathways and promoter elements regulating cyclooxygenase-2 gene expression in endotoxic-treated macrophage/monocytic cells. *J.Biol.Chem.*, 276, 3977-3982.
- Meyer, M., Clauss, M., Lepple-Wienhues, A., *et al.* (1999). A novel vascular endothelial growth factor encoded by Orf virus, VEGF-E, mediates angiogenesis via signaling through VEGFR-2 (KDR) but not VEGFR-1 (Flt-1) receptor tyrosine kinases. *EMBO.J.*, 18, 363-374.
- Millauer, B., Shawver, L.K., Plate, K.H., *et al.* (1994). Glioblastoma growth inhibited in vivo by a dominant-negative Flk-1 mutant. *Nature*, 367, 576-579
- Min, H.Y., Doyle, L.V., Vitt, C.R., *et al.* (1996). Urokinase receptor antagonists inhibit angiogenesis and primary tumor growth in syngeneic mice. *Cancer Res.*, 56, 2428-2433.
- Mineta, H., Miura, K., Ogino, T., *et al.* (2000). Prognostic value of vascular endothelial growth factor (VEGF) in head and neck squamous cell carcinomas. *Br.J.Cancer*, 83,775-781.
- Montesano, R, Orci, L, Vassali, P., *et al.* (1983). *In vitro* rapid organization of endothelial cells into capillary-like networks is promoted by collagen matrices. *J.Cell Biol.*, 97, 1648-1652.
- Morales-Ruiz, M., Fulton, D., Sowa, G., *et al.* (2000). Vascular endothelial growth factor-stimulated actin reorganization and migration of endothelial cells is regulated via the serine/threonine kinase Akt. *Circ.Res.*, 86, 892-896.
- Mukhopadhyay, D., Tsiokas, L. and Sukhatme, V.P. (1995). Wild-type p53 and v-Src exert opposing influences on human vascular endothelial growth factor gene expression. *Cancer Res.*, 55, 6161-6165.
- Murohara, T., Horowitz, J.R., Silver, M., *et al.* 1998). Vascular endothelial growth factor/vascular permeability factor enhances vascular permeability via nitric oxide and prostacyclin. *Circulation*, 97, 99-107.

- Nageswari, K., Yamaguchi, S., Yamakawa, T., Niimi, H. (2002). Quantitative assessment of cerebral neocapillary network and its remodeling in mice using intravital fluorescence videomicroscopy. *Angiogenesis*, 5, 99-105.
- Nakata, S., Ito, K., Fujimori, M., *et al.* (1998). Involvement of vascular endothelial growth factor and urokinase-type plasminogen activator receptor in microvessel invasion in human colorectal cancers. *Int.J.Cancer.*, 79, 179-186.
- Neufeld, G., Cohen, T., Gengrinovitch, S., *et al.* (1999). Vascular endothelial growth factor (VEGF) and its receptors. *FASEB.J.*, 13, 9-22.
- Nihiro, H., Otsuka, T., Izuhara, K., *et al.* (1997). Regulation by interleukin-10 and interleukin-4 of cyclooxygenase-2 expression in human neutrophils. *Blood*, 89, 1621-1628.
- Niimi, H., Nageswari, G., Ranade, S., *et al.* (2000). Microcirculatory characterization of cerebral angiogenesis in mice using intravital videomicroscopy. *Clin.Hemorheol.Microcirc.*, 23, 293-301.
- Niimi, H., *et al.*, (2003). Cerebral angiogenesis induced by growth factor: intravital microscopic studies using models. *Clin.Hemorheol.Microcirc.*, 19, 149-156.
- Okada, F., Rak, J., St. Croix, B., *et al.* (1998). Impact of oncogenes on tumor angiogenesis: mutant K-ras upregulation of VEGF/VPF is necessary but not sufficient for tumorigenicity of human colorectal carcinoma cells. *Proc.NatlAcad.Sci.U.S.A.*, 95, 3609-3614.
- Onoe, Y., Miyaura, C., Kaminakayashiki, T., *et al.* (1996). IL-13 and IL-4 inhibit bone resorption by suppressing cyclooxygenase-2-dependent prostaglandin synthesis in osteoblasts. *J.Immunol.*, 156, 758-764.
- Ortega, N., Hutchings, H., Plouet, J., *et al.* (1999). Signal relays in the VEGF system. *Front.Biosci.*, 4, D141-152.
- Ortega, N., Jonca F., Vincent, S., *et al.*, (1997). Systemic activation of the vascular endothelial growth factor receptor KDR/flk-1 selectively triggers endothelial cells with an angiogenic phenotype. *Am.J.Pathol.*, 151, 1215-1224.
- Oshima, M., Dinchuk, J.E., Kargman, S.L., *et al.* (1996). Suppression of intestinal polyposis in APC^{Δ716} knockout mice by inhibition of prostaglandin endoperoxide synthase-2 (COX-2). *Cell*, 87, 803-809.

- Pan, M.H., Huang, T.M. and Lin, J.K. (1999). Biotransformation of curcumin through reduction and glucuronidation in mice. *Drug Metab.Disposit.*, 27, 486-494.
- Papapetropoulos, A., Garcia-Cardena, G., Madri, J.A., *et al.* (1997). Nitric oxide contributes to the angiogenic properties of vascular endothelial growth factor in human endothelial cells. *J.Clin.Invest.*, 100, 3131-3139.
- Patz, A. (1980). Studies on retinal neovascularization. Friedenwald Lecture *Invest. Ophthalmol. Vis. Sci.*, 19, 1133-1138.
- Pepper, M.S., Montesano, R., Mandriota, S., *et al.* (1996). Angiogenesis: a paradigm for balanced extracellular proteolysis during cell migration and morphogenesis. *Enzyme Protein.*, 49, 138-162.
- Persico, M. G., Vincenti, V. and DiPalma, T. (1999). *Structure, expression and receptorbinding properties of placenta growth factor (PlGF)*. In: L. Claesson-Welsh (ed.), *Vascular Growth Factors and Angiogenesis*, 31-40. Berlin: Springer-Verlag.
- Pereira, M.A., Grubbs, C.J., Barnes, L.H., *et al.* (1996). Effects of the phytochemicals, curcumin and quercetin, upon azoxymethane-induced colon cancer and 7,12-dimethylbenz[*a*]anthracene-induced mammary cancer in rats. *Carcinogenesis*, 17, 1305-1311.
- Plate, K.H., Breier, G., Weich, H.A., *et al.* (1992). Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo. *Nature (Lond.)*, 359, 845-848.
- Plummer, S.M., Holloway, K.A., Manson, M.M., *et al.* (1999). Inhibition of cyclooxygenase-2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF- κ B activation via the NIK/IKK signaling complex. *Oncogene*, 18, 6013-6020.
- Ramsay, R.G., Thompson, M.A., Hayman, J.A., *et al.* (1992). Myb expression is higher in malignant human colonic carcinoma and premalignant adenomatous polyps than in normal mucosa. *Cell.Growth.Differ.*, 3, 723-730.
- Ramsay, R.G., Friend, A., Vizantios, Y., *et al.* (2000). Cyclooxygenase-2, a colorectal cancer nonsteroidal anti-inflammatory drug target, is regulated by c-MYB. *Cancer Res.*, 60, 1805-1809.

- Rao, C.V., Rivenson, A., Simi, B., *et al.* (1995). Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. *Cancer Res.*, 55, 259-266.
- Ravindranath, V., and Chandrasekhara, N. (1980). Absorption and tissue distribution of curcumin in rats. *Toxicology*, 16, 259-265.
- Reddy, A.C.P. and Lokesh, B.R. (1992). Studies on spice principles as antioxidants in the inhibition of lipid peroxidation of rat liver microsomes. *Mol.Cell Biochem.*, 111, 117-124.
- Reddy, B.S., Hirose, Y., Lubet, R., *et al.* (2000). Chemoprevention of colon cancer by specific cyclooxygenase-2 inhibitor, Celecoxib, administered during different stages of carcinogenesis. *Cancer Res.*, 60, 293-297.
- Ristimaki, A., Honkanen, N., Jankala, H., *et al.* (1997). Expression of cyclooxygenase-2 in human gastric carcinoma. *Cancer Res.*, 57, 1276-1280.
- Rosenberg, L., Plamer, J.R., Zauber, A.G., *et al.* (1991). A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. *J.Natl.Cancer Inst.*, 83, 355-358.
- Sano, H., Kawahito, Y., Wilder R.L., *et al.* (1995). Expression of cyclooxygenase-1 and-2 in human colorectal cancer. *Cancer Res.*, 55, 3785-3789.
- Sambaiah, K., Ratankumar, S., Kamanna, V.S., *et al.* (1982). Influence of tumeric and curcumin on growth, blood constituents, and serum enzymes in rats. *J.Fed.Sci.Technol.*, 19, 187-190.
- Sawaoka, H., Tsuji, S., Tsijii, M., *et al.*, (1999). Cyclooxygenase inhibitors suppress angiogenesis and reduced tumor growth *in vivo*. *Lab.Invest.*, 79, 1469-1477.
- Schrey, M.P. and Patel, K.V. (1995). Prostaglandin E2 production and metabolism in human breast cancer cells and breast fibroblasts. Regulation by inflammatory mediators. *Br.J.Cancer.*, 72, 1412-1419.
- Schmedthe, J.F., Ji, y.S., Liu, W.L., *et al.* (1997). Hypoxia induces cyclooxygenase-2 via the NF- κ B p65 transcription factor in human vascular endothelial cells. *J.Biol.Chem.*, 272, 601-608
- Sebti, S.M. and Hamilton, A.D. (2000). Design of growth factor antagonists with antiangiogenic and antitumor properties. *Oncogene*, 19, 6566-6573.

- Senger, D.R., Brown, L.F., Claffey, K.P., *et al.* (1994). Vascular permeability factor, tumor angiogenesis and stroma generation. *Invasion.Metastasis.*, 14, 385-394.
- Senger, D.R., Ledbetter, S.R., Claffey, K.P., *et al.* (1996). Stimulation of endothelial cell migration by vascular permeability factor/vascular endothelial growth factor through cooperative mechanisms involving the α v β 3 integrin, osteopontin, and thrombin. *Am.J.Pathol.*, 149, 293-305.
- Senger, D.R., Claffey, K.P., Benes, J.E., *et al.* (1997). Angiogenesis promoted by vascular endothelial growth factor: regulation through α 1 and α 2 β 1 integrins. *Proc.Natl Acad.Sci.U.S.A.*, 94, 13612-13617.
- Sharma, R.A., Manson, M.M., Gescher, A., *et al.* (2001). Colorectal cancer chemoprevention: biochemical targets and clinical development of promising agents. *Eur.J.Cancer.*, 37, 12-22.
- Sheng, H., Shao, J., Kirkland, S.C., *et al.* (1997). Inhibition of human colon cancer cell growth by selective inhibition of cyclooxygenase-2. *J.Clin.Invest.*, 99, 2254-2259.
- Sheng, H., Shao, J., Morrow, J.D., *et al.* (1998). Modulation of apoptosis and Bcl-2 expression by prostaglandin E₂ in human colon cancer cells. *Cancer Res.*, 58, 362-366.
- Shibuya, M., Yamaguchi, S., Yamane, A., *et al.* (1990). Nucleotide sequence and expression of a novel human receptor type tyrosine kinase gene (*flt*) closely related to the *fms* family. *Oncogene*, 5, 519-524.
- Shibuya, M., Ito, N., and Claesson-Welsh, L. (1999). Structure and function of vascular endothelial growth factor receptor-1 and -2. *Curr.Top.Microbiol. Immunol.*, 237, 59-83.
- Shih, C.A. and Lin, J.K. (1993). Inhibition of 8-hydroxydeoxyguanosine formation by curcumin in mouse fibroblast cells. *Carcinogenesis*, 14:709-712.
- Shoba, G., Joy, D., Joseph, T., *et al.* (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med.*, 64, 353-356.
- Shweiki, D., Itin, A., Soffer, D., *et al.* (1992). Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature*, 359, 843-845.

- Singh, S.V., Hu, X., Srivastava, S.K., *et al.* (1998) Mechanism of inhibition of benzo[*a*]pyrene-induced forestomach cancer in mice by dietary curcumin. *Carcinogenesis*, 19, 1357–1360.
- Singletary, K., MacDonald, C., Iovinelli, M., *et al.* (1998) Effect of the β -diketones diferuloyl methane (curcumin) and dibenzoylmethane on rat mammary DNA adducts and tumors induced by 7,12-dimethylbenz[*a*]anthracene. *Carcinogenesis*, 19, 1039–1043.
- Smith, W.L., Garavito, R.M., and DeWitt, D.L. (1996). Prostaglandin endoperoxide H synthase (cyclooxygenase)-1 and -2. *J.Biol.Chem.*, 271, 33157-33160.
- Soff, G.A., Sanderowitz, J., Gately, S., (1995). Expression of plasminogen activator inhibitor type 1 by human prostate carcinoma cells inhibits primary tumor growth, tumor-associated angiogenesis, and metastasis to lung and liver in an athymic mouse model. *J.Clin.Invest.*, 96, 2593-2600.
- Soni, K.B., and Kuttan, R. (1992). Effect of oral curcumin administration on serum peroxides and cholesterol levels in human volunteers. *Indian J.Physiol.Pharmacol.*, 36, 273-275.
- Song, Z.J., Gong, P. and Wu, Y.E. (2002). Relationship between the expression of iNOS, VEGF, tumor angiogenesis and gastric cancer. *World J.Gastroenterol.*, 8 (4), 591-5.
- Souza, R.F., Shewmake, K., Beer, D.G., *et al.* (2000). Selective inhibition of cyclooxygenase-2 suppresses growth and induces apoptosis in human esophageal adenocarcinoma cells. *Cancer Res.*, 60, 5767-5772.
- Sreejayan, and Rao, M.N.A. (1994). Curcuminoids as potent inhibitors of lipid peroxidation. *J.Pharm.Pharmacol.*, 46:1013-1016.
- Srimal, R.C., and Dhawan, B.N. (1985). *Pharmacological and clinical studies on Curcuma longa*, Hamard Natl. Found. Monograph, New Delhi, India, Section 3B(ii) : 131-138.
- Stockhammer, G., Obwegeser, A., Kostron, H., *et al.* (2000). Vascular endothelial growth factor (VEGF) is elevated in brain tumor cysts and correlates with tumor progression. *Acta.Neuropathol.(Berl.)*, 100, 101-105.
- Stromblad, S., Becker, J.C., Yebra, M., *et al.* (1996). Suppression of p53 activity and p21WAF1/CIP1 expression by vascular cell integrin α V β 3 during angiogenesis. *J.Clin.Invest.*, 98, 426-433.

- Subbaramaiah, K., Chung, W.J., and Dannenberg, A.J. (1998). Caramide regulates the transcription of cyclooxygenase-2. Evidence for involvement of extracellular signal-regulated kinase/c-Jun N-terminal kinase and p38 mitogen-activated protein kinase pathways. *J.Biol.Chem.*, 273, 32943-32949.
- Subramanian, M., Sreejayan Rao, M.N.A., Devasagyam, T.P.A. *et al.* (1994) Diminution of singlet oxygen-induced DNA-damage by curcumin and related antioxidants. *Mutat.Res.*, 311:249-255.
- Sumiyoshi, Y., Yamashita, Y., Maekawa, T., *et al.* (2000). Expression of CD4, vascular endothelial growth factor, and proliferating cell nuclear antigen in severe venous invasional colorectal cancer and its relationship to liver metastasis. *Surg.Today*, 30, 323-327.
- Takahashi, Y., Kitadai, Y., Bucana, C.D., *et al.* (1995). Expression of vascular endothelial growth factor and its receptor, KDR, correlates with vascularity, metastasis, and proliferation of human colon cancer. *Cancer Res.*, 55, 3964-3968.
- Tanaka, T., Makita, H., Ohnishi, M., *et al.* (1994) Chemoprevention of 4-nitroquinoline 1-oxide-induced oral carcinogenesis by dietary curcumin and hesperidin: comparison with the protective effect of beta-carotene. *Cancer Res.*, 54, 4653-4659.
- Tang, H., Kerins, D.M., Hao, Q., *et al.* (1998). The urokinase-type plasminogen activator receptor mediates tyrosine phosphorylation of focal adhesion proteins and activation of mitogen-activated protein kinase in cultured endothelial cells. *J.Biol Chem.*, 273, 18268-18272.
- Teraoka, H., Sawada, T., Nishihara, T., *et al.* (2001). Enhanced VEGF production and decreased immunogenicity induced by TGF- β 1 promote liver metastasis of pancreatic cancer. *Br.J.Cancer*, 85, 612-617.
- Terman, B. I., Carrion, M. E., Kovacs, E., *et al.* (1991). Identification of a new endothelial cell growth factor receptor tyrosine kinase. *Oncogene*, 6, 1677-1683.
- Thun, M.T., Namboodiri, M.M. and Healt, C.W. (1991). Aspirin use and reduced risk of fatal colon cancer. *N.Engl.J.Med.*, 11, 593-596.

- Tian, H., McKnight, S.L. and Russel, D.W. (1997). Endothelial PAS domain protein I (EPAS1), a transcription factor selectively expressed in endothelial cells. *Genes.Dev.*, 11, 72-82.
- Toi, M., Hoshima, S., Takayanagi, T. and Tominaga, T. (1994). Association of vascular endothelial growth factor expression with tumor angiogenesis and with early relapse in primary breast cancer. *Jpn.J.Cancer Res.*, 85, 1045-1049.
- Tomozawa, S., Tsuno, N.H., Sunami, E., *et al.* (2000). Cyclooxygenase-2 overexpression correlates with tumor recurrence, especially haematogenous metastasis, of colorectal cancer. *Br.J.Cancer.*, 83, 324-328.
- Tsuji, M. and DuBois, R.N. (1995). Alteration in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. *Cell*, 83, 493-501.
- Tsuji, M., Kawano, S., and DuBois, R.N. (1997). Cyclooxygenase-2 expression in human colon cancer cells increase metastasis potential. *Proc.Natl.Acad.Sci. U.S.A.*, 94, 3336-3340.
- Tsuji, M., Kawano, S., Tsuji, S., *et al.* (1998). Cyclooxygenase regulates angiogenesis induced by colon cancer cells [(1998). published erratum appears in *Cell.*, 94, 271], *Cell*, 93, 705-716.
- Tsuji, T., Sasaki, Y., Tanaka, M., *et al.* (2002). Microvessel morphology and vascular endothelial growth factor expression in human colonic carcinoma with or without metastasis. *Lab.Invest.*, 85, 555-562.
- Uefuji, K., Ichikura, T., and Mochizuki, H. (2000). Cyclooxygenase-2 expression is related to prostaglandin biosynthesis and angiogenesis in human gastric cancer. *Clin.Cancer.Res.*, 6,135-138.
- Veikkola, T., Karkainen, M., Claesson-Welsh, L., *et al.*, (2000). Regulation of angiogenesis via vascular growth factor receptors. *Cancer research.*, 60, 203-212.
- Wakui, S., Furusato, M., Sasaki, H., *et al.* (1992). Tumor angiogenesis in prostatic carcinoma with and without bone metastasis: a morphometric study. *J.Pathol.*, 168, 257-262.
- Warren, R.S., Yaun, H., Matli, M.R., *et al.* (1995). Regulation of vascular endothelial growth factor of human colon cancer tumorigenesis in a mouse model of experimental liver metastasis. *J.Clin.Investig.*, 95, 1789-1797.

- Webster, K.A., Discher, D.J., and Bishopric, N.H. (1994). Regulation of fos and jun immediate early gene by redox or metabolic stress in cardiac myocytes. *Circ.Res.*, 74, 679-686.
- Weidner, N., Semple, J.P., Welch, W.R., *et al.* (1991). Tumor angiogenesis and metastasis – correlation in invasive breast carcinoma. *N.Engl.J.Med.*, 324, 1-8.
- Williams, C.S., Tsujii, M., Reese, J., *et al.* (2000). Host cyclooxygenase-2 modulates carcinoma growth. *J.Clin.Invest.*, 105:1589-1594.
- Wolff, H., Saukkonen, K., Anttila, S., *et al.* (1998). Expression of cyclooxygenase-2 in human lung carcinoma. *Cancer Res.*, 58, 4997-5001.
- Xiong, B., Sun, T., Yuan, H., Hu, M., Hu, W., Cheng, F. (2003). Cyclooxygenase-2 expression and angiogenesis in colorectal cancer. *World J.Gastroenterol*, 9, 1237-1240.
- Yan, S.F., Tritto, I., Pinsky, D., *et al.* (1995). Induction of interleukin-6 (IL-6) by hypoxia in vascular cells. Central role of the binding site for nuclear factor-IL-6. *J.Biol.Chem.*, 270, 11463-11471.
- Yang, X., Sheares, K.K., Davie, V., *et al.* (2002). Hypoxic induction of cox-2 regulates proliferation of human pulmonary artery smooth muscle cells. *Am. J.Respir.Cell Mol.Biol.*, 27, 688-692.
- Yokoyama, C., Takai, T., and Tanabe, T. (1988). Primary structure of sheep prostaglandin endoperoxide synthase deduced from cDNA sequence. *FEBS Lett.*, 231, 347-351.
- Yoshikawa, T., Tsuburaya, A., Kobayashi, O., *et al.* (2000). Plasma concentrations of VEGF and bFGF in patients with gastric carcinoma. *Cancer Lett.*, 153:7-12.
- Zhang, F., Altorki, N.K., Mestre, J.R., *et al.* (1999). Curcumin inhibits cyclooxygenase-2 transcription in bile acid-and phorbol ester-treated human gastrointestinal epithelial cells. *Carcinogenesis.*, 20, 445-451.
- Ziche, M., *et al.* (1994). Nitric oxide mediates angiogenesis in vivo and endothelial cell growth and migration in vitro promoted by substance P. *J.Clin.Invest.*, 94 (5), 2036-2044.
- Ziche, M., Morbidelli, L., Choudhuri, R., *et al.* (1997). Nitric oxide synthase lies downstream from vascular endothelial growth factor-induced but not basic fibroblast growth factor-induced angiogenesis. *J.Clin.Invest.*, 99, 2625-2634.



APPENDICES

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APPENDIX A

Buffers and Reagents

SDS-PAGE

Stock acrylamide

| | | |
|----------------------------|-----|----|
| Acrylamide | 15 | g |
| N,N-methylenebisacrylamide | 0.4 | g |
| DW | 50 | ml |

Lower gel tris

| | | |
|-----------|-------|----|
| Tris-base | 3.643 | g |
| SDS | 0.080 | g |
| DW | 20 | ml |

Adjust to pH 8.8 with 12 N HCL and filter through 0.45 μ l membrane

Upper gel tris

| | | |
|-----------|-------|----|
| Tris-base | 1.204 | g |
| SDS | 0.080 | g |
| DW | 20 | ml |

Adjust to pH 6.8 with 12 N HCL and filter through 0.45 μ l membrane

Sample buffer (dye marker)

| | | |
|-----------------|--------|----|
| Tris-HCL | 0.0985 | g |
| SDS | 0.4 | g |
| Glycerol | 1 | ml |
| 2-ME | 0.5 | g |
| Bromphenol blue | 10 | mg |

Adjust to pH 6.8 using 1 N NaOH and add DW to 10 ml

2 % Ammonium persulfate

| | | |
|---------------------|----|----|
| Ammonium persulfate | 40 | mg |
| DW | 2 | ml |

Seperating gel 7.5 %

| | | |
|-------------------------|------|---------|
| Stock acrylamide | 0.85 | ml |
| Lower gel tris | 0.85 | ml |
| DW | 1.53 | ml |
| TEMED | 2.72 | μ l |
| 2 % Ammonium persulfate | 0.17 | ml |

Stacking gel 5 %

| | | |
|-------------------------|-------|---------|
| Stock acrylamide | 0.332 | ml |
| Lower gel tris | 0.5 | ml |
| DW | 1.12 | ml |
| TEMED | 2 | μ l |
| 2 % Ammonium persulfate | 40 | μ l |

Electrophosis buffer (running buffer)

| | | |
|-----------|------|----|
| Tris-base | 1.2 | g |
| Glycine | 5.76 | g |
| SDS | 0.4 | g |
| DW | 400 | ml |

Coomassie Staining

| | | |
|----------------------------|------|----|
| Stain | | |
| Coomassie Brilliant Blue R | 0.91 | g |
| Acetic acid | 45 | ml |

| | | |
|------|-----|----|
| MeOH | 215 | ml |
| DW | 240 | ml |

Destain

| | | |
|-------------|-----|----|
| Acetic acid | 90 | ml |
| MeOH | 430 | ml |
| DW | 480 | ml |

Amido black staining**Stain**

| | | |
|-------------|------|----|
| Amido black | 0.01 | g |
| MeOH | 45 | ml |
| Acetic acid | 10 | ml |
| DW | 45 | ml |

Destain

| | | |
|-------------|----|----|
| MeOH | 90 | ml |
| Acetic acid | 2 | ml |
| DW | 8 | ml |

WESTERN BLOT REAGENTS**Protein Transfer Buffer , pH 8.3**

| | | |
|-----------|------|----|
| Tris-base | 1.93 | g |
| Glycine | 9.0 | g |
| DW | 1000 | ml |

20x Tris-Buffer Saline (TBS), pH 7.5

| | | |
|-----------|--------|----|
| Tris-base | 24.228 | g |
| NaCl | 175.32 | g |
| DW | 1000 | ml |

TTBS (0.05 % Tween 20)

| | | |
|----------|------|----|
| Tween 20 | 0.5 | ml |
| TBS | 1000 | ml |

Blocking Solution (5 % non-fat dried milk, 2 % BSA)

| | | |
|------|-----|----|
| Milk | 5 | g |
| BSA | 2 | g |
| TBS | 100 | ml |

ECL REAGENTS**90 mM p-Coumaric acid stock solution**

| | | |
|-----------------|-------|----|
| p-Coumaric acid | 0.015 | g |
| DMSO | 1 | ml |

Store in the dark at 4 °C

250 mM Luminol stock solution

| | | |
|---------|-------|----|
| Luminol | 0.043 | g |
| DMSO | 1 | ml |

Store in the dark at 4 °C

100 mM tris pH 8.0, sterilize by autoclaving

| | | | |
|------------------|-----------------------------------|--------|---------|
| Tris | | 1.2114 | g |
| BW | | 100 | ml |
| Solution A: 5 ml | 100 mM tris pH 8.0 | 5 | ml |
| | 90 mM Coumaric acid | 22 | μ l |
| | 250 mM Luminol | 50 | μ l |
| Solution B: 5 ml | 100 mM tris pH 8.0 | 5 | ml |
| | 3 % H ₂ O ₂ | 30 | μ l |



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APPENDIX B

Image processing Global Lab Image/2 (GLI/2) software

1. Main application of Windows

The main Window of this program shown in Figure A.

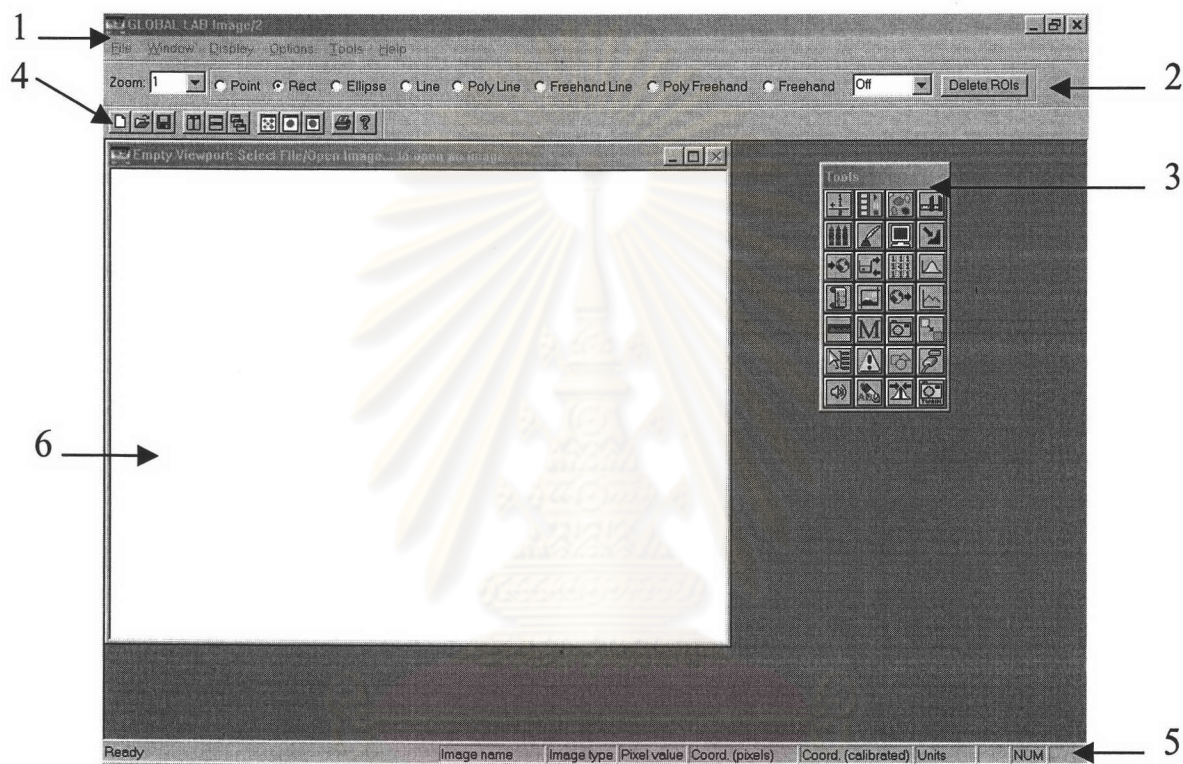


Figure A. Main Window of GLI/2

1. File Menu Options
2. ROI Type
3. Tool box
4. Toolbar
5. Status Bar
6. Viewport

1.1. File Menu Options

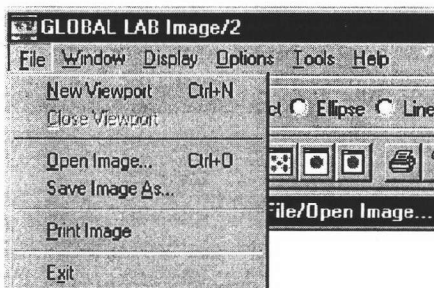


Figure B

New Viewport

Select this option to create a new viewport so that you can view an image. The new viewport becomes the active viewport.

Close Viewport

Select this option to close the active viewport and delete any ROIs attached to the viewport.

Open Image

Select this option to open an image from disk. The image must be stored in standard Windows bitmap format (noncompressed). The image can be opened as a binary, 8-bit grayscale, 16-bit grayscale, 32-bit grayscale, floating-point grayscale, 24-bit RGB (Red/Green/Blue), or 24-bit HSL (Hue/Saturation/Luminance) color image. By default, the image is opened as an 8-bit grayscale image.

Save Image As

Select this option to save the image in the active viewport as a standard Windows bitmap file.

Print Image

Select this option to print the image exactly as it is seen in the active viewport. Zoomed images print exactly as seen. Images are printed as large as possible while keeping their aspect ratios.

Exit

Select this option to close the application and all open tools.

1.2. ROI Type

The ROI type can be specified by using the ROI menu bar which refer to Figure C or Options / ROI Type from the main application. The ROI Manager tool shown in Figure D.

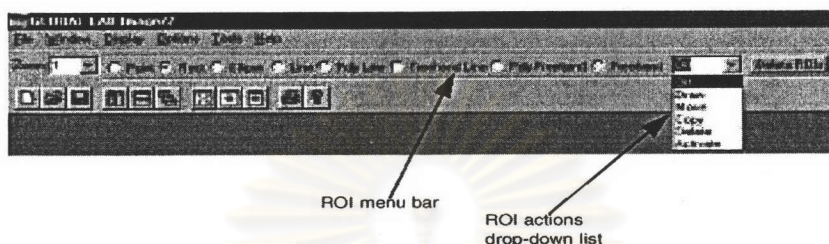


Figure C

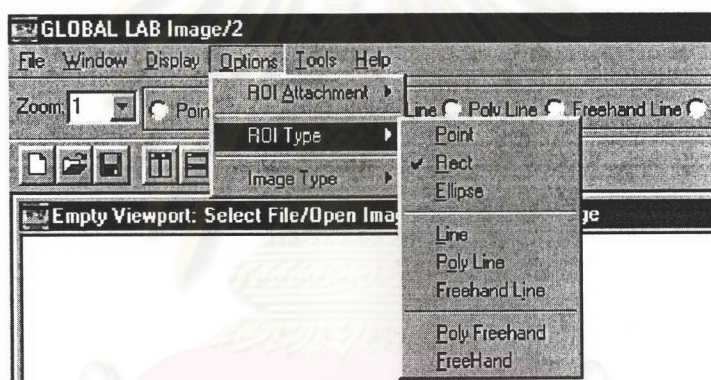


Figure D

An ROI is a region of interest. It is the portion of an image to manipulate. This section contains additional information about ROIs.

GLI/2 provides eight different types of ROIs. Each ROI is created, moved, copied, selected, used, and deleted in the same way. The ROI type that has been selected determines the type of ROI that is created.

An ROI is a region of interest. It is the portion of an image that you want to manipulate. This section contains additional information about ROIs.

GLI/2 supports the following types of ROIs: Point, Rectangle, Ellipse, Line, and Poly line.

1.3. Toolbox

The Toolbox and Tools/show Toolbox from the main application that holds all the loaded tools were shown in Figure E and F, respectively. To use a tool in the Toolbox, click on the tool icon.



Figure E



Figure F

1.4. Toolbar



Figure G

The first three buttons on the toolbar correspond to the following menu options: File /New viewport, File/Open Image, File/Save Image As.

The next three buttons on the toolbar correspond to the following menu options: Window /Tile Vertical, Window /Tile Horizontal, Window/Cascade

The next three buttons on the toolbar correspond to the following menu options: Display/Image Display Mode/Size Image to Viewport, Display/Image Display Mode/Show Image Actual Size, Display/Image Display Mode/Fit Viewport to Image

The last two buttons on the toolbar correspond to the following: File/ Print Image menu option, Shows the About box for GLI/2

1.5. Status Bar

The status bar is displayed in the lower right corner of the main application window. An example status bar is shown in Figure H.

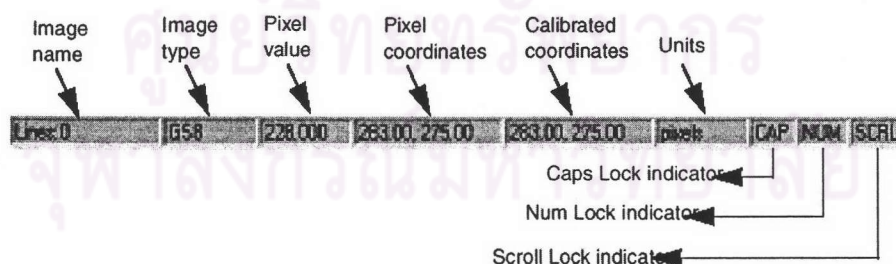


Figure H

The items shown in the status bar are described as follows:

Image name – the name of the image in the active viewport.

Image type – the type of image in the active viewport

Pixel value – the value of the pixel at the current cursor location.

Pixel coordinates – the location (x, y) of the pixel at the current cursor location, where 0,0 refers to the lower-left corner of the image.

Calibrated coordinates – the location (x, y) of the pixel at the current cursor location in calibrated units (if the image has an attached calibration object).

Units – the unit of measure that GLI/2 uses to perform its calculations. By default, GLI/2 uses pixel measurements. If the image has an attached calibration object, GLI/2 displays the measurements in calibrated units.

Caps Lock indicator – CAPS indicates that the Caps Lock key is ON (alphabetic characters on the keyboard are shifted to uppercase).

Num Lock indicator – NUM indicates that the Num Lock key is ON (the numeric keypad on the keyboard is activated).

Scroll Lock indicator – SCRL indicates that the Scroll Lock key is ON (the cursor control keys on the keyboard are affected).

1.6. Viewport

A viewport is a window in which to view an image. Each viewport contains a view and a title bar. The view portion of the viewport is the portion actually showing the image. The title bar contains information about the viewport. Viewports also have scrollbars that you can be used to move the image around if the image does not fit inside the viewport. Figure I shows open viewports with image eNOS standard.

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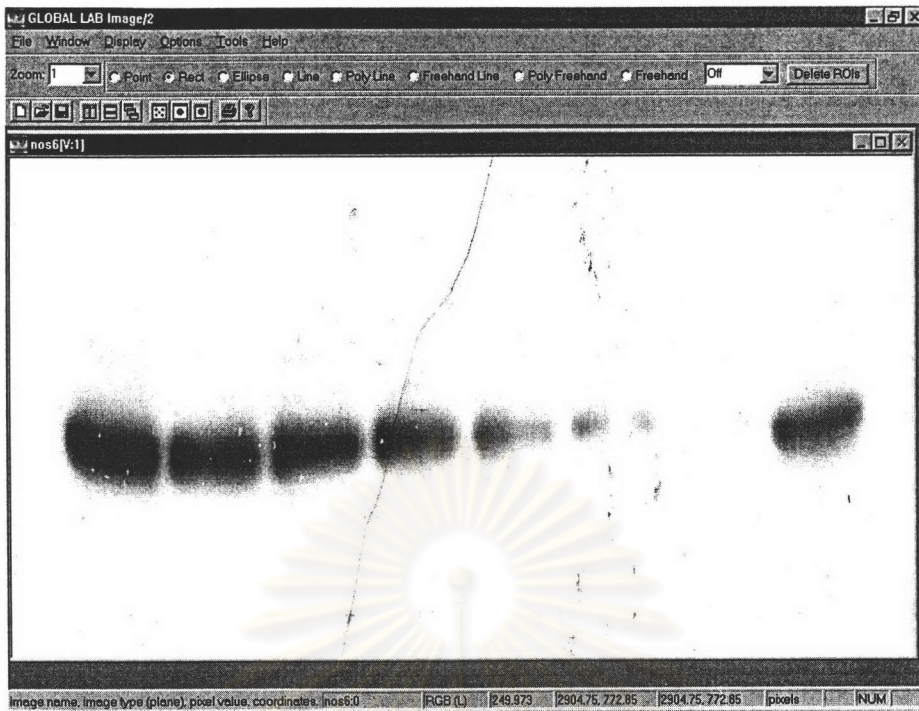



Figure I

2. Using the File Manager Tool

To open a File Manager Tool, select the  icon from the Toolbox or select File Manager from the Tools menu (see Figure J).

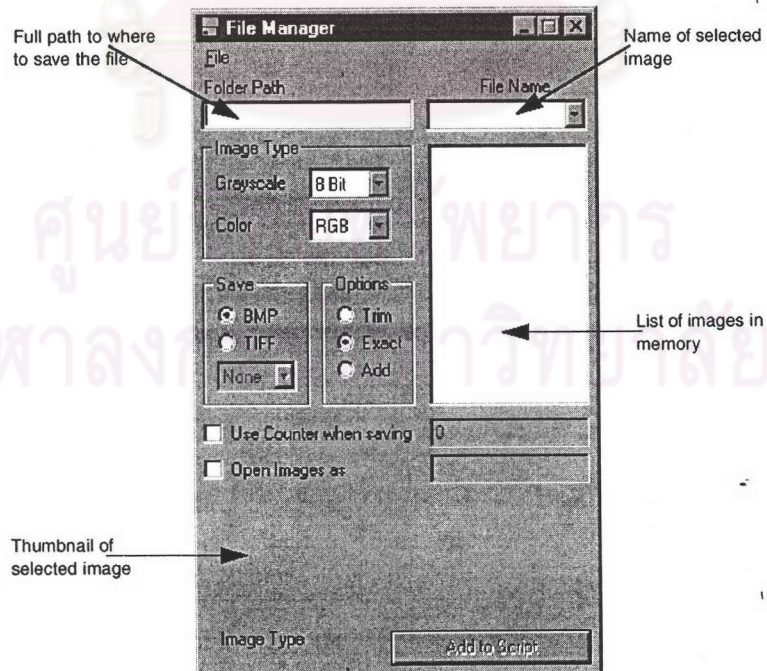



Figure J

File Manager Tool allows to open many popular file formats. It also open a mixture of color and grayscale images of different image types without being concerned with file conversion.

3. Using the Edge Finder Tool

To open an Edge Finder Tool, select the  icon from the Toolbox or select Edge Finder from the Tools menu (see Figure K).

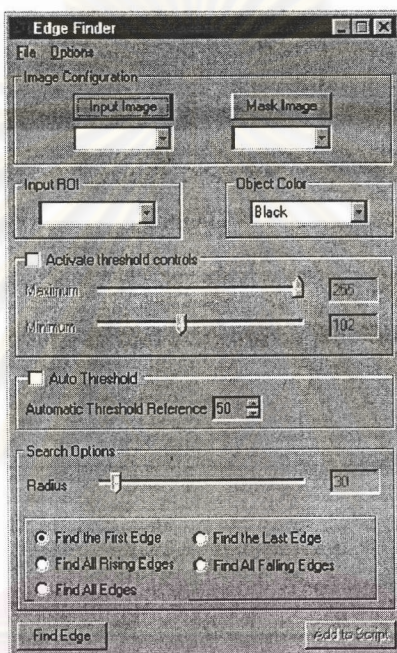



Figure K

The Edge Finder Tool allows to extract points, edges, or contours from a binary image.

4. Using the Histogram Tool

To open a Histogram Tool, select the  icon from the Toolbox or select Histogram from the Tools menu (see Figure L).

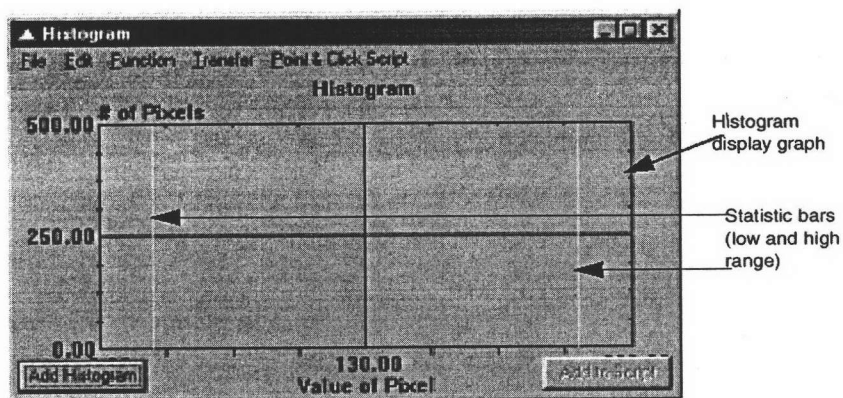


Figure L

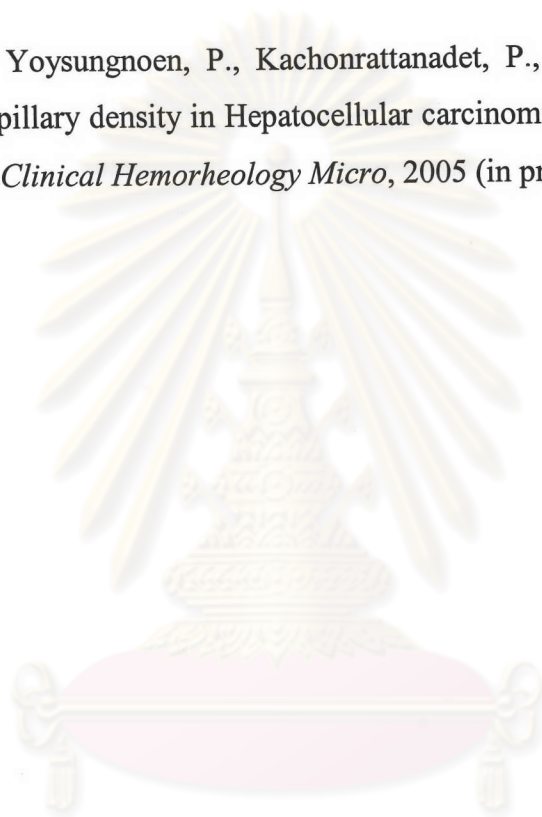
The Histogram Tool allows to create histograms of images. Up to 100 histograms can be loaded to the same graph. The histograms can be added from multiple images and from multiple viewports. Histogram data can be transferred directly to the Microsoft Excel worksheet program.

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APPENDIX C

Lists of Publications

1. Yoysungnoen, P., Wirachwong, P., Bhattarakosol, P., Niimi, H., and Patumraj S. Antiangiogenic activity of curcumin in Hepatocellular carcinoma cells implanted nude mice. *Clinical Hemorheology Micro*, 2005 (in press).
2. Patumraj S., Yoysungnoen, P., Kachonrattanadet, P., and Wirachwong, P. Tumor neocapillary density in Hepatocellular carcinoma cells implanted nude mice model. *Clinical Hemorheology Micro*, 2005 (in press).



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BIOGRAPHY

| | |
|------------------------------|---|
| NAME | Miss Pornprom Yoysungnoen |
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| INSTITUTIONS ATTENDED | Khonkaen University, 1988-1991: Bachelor of Nursing Changmai University, 1993-1997: Master of Science (Physiology) Chulalongkorn University, 2000-2004 Ph.D. candidate (Physiology) |
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| RESEARCH GRANTS | Thai Asahi Glass Foundation Chulalongkorn University and the Ministry of University Affairs, Thailand |

LISTS OF PUBLICATIONS

1. Yoysungnoen, P., Wirachwong, P., Bhattarakosol, P., Niimi, H., and Patumraj S. Antiangiogenic activity of curcumin in Hepatocellular carcinoma cells implanted nude mice. *Clinical Hemorheology Micro*, 2005 (in press).
2. Patumraj S., Yoysungnoen, P., Kachonrattanadet, P., and Wirachwong, P. Tumor neocapillary density in Hepatocellular carcinoma cells implanted nude mice model. *Clinical Hemorheology Micro*, 2005 (in press).



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